Vascepa® (icosapent ethyl) as an adjunct to diet and in combination with a statin to reduce TG, non-HDL-C, ApoB, LDL-C, TC, and VLDL-C in adult patients with mixed dyslipidemia and CHD or a CHD risk equivalent

Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)

October 16, 2013

Introduction

Peggy Berry

VP, Regulatory Affairs

Amarin Pharma

Proposed Vascepa® (icosapent ethyl) Indication – Dosed at 4g/day

- Vascepa (icosapent ethyl)
  - Highly purified ethyl-EPA
- In adult patients with mixed dyslipidemia
- Adjunct to diet and statin therapy to reduce triglycerides, non-HDL-C, ApoB, LDL-C, TC and VLDL-C
- At high CHD risk (per ATP III Guidelines)
  - Coronary artery disease
  - Manifestations of CHD
  - Diabetes

Hypertriglyceridemia Clinical Program for Vascepa

	MARINE (N=229)	ANCHOR (N=702)	REDUCE-IT (N~8000)
Patients	Severe Hyper-triglyceridemia	Mixed dyslipidemia on statin	Mixed dyslipidemia on statin
CV Risk		High risk for CHD event	High risk for CHD event
TG Level	≥500 mg/dL	200 to <500 mg/dL	150 to <500 mg/dL
Primary Endpoint	TG reduction	TG reduction	CV Events
Timing (Yrs)	2009-2011	2009-2011	2011-ongoing
Status	Approved	Under Review	>6000 pts randomized

All Vascepa Studies Conducted under SPA Agreements

- Agreement included primary and secondary endpoints, recruitment criteria & planned analysis
  - MARINE
  - ANCHOR
  - REDUCE-IT

Vascepa Agenda

Unmet Need	**Michael Miller, MD** Director, Center for Preventive Cardiology University of Maryland Medical Center
ANCHOR Efficacy	**Declan Doogan, MD** Chief Medical Officer Amarin Pharma
Safety & REDUCE-IT Overview	**Steven Ketchum, PhD** President of Research and Development Amarin Pharma
Clinical Interpretation & Benefit-risk	**Harold Bays, MD** Medical Director / President Louisville Metabolic & Atherosclerosis Research Center

Additional Experts

Brent Blumenstein, PhD	Principal Biostatistical Consultant Trial Architecture Consulting
Howard Weintraub, MD	Clinical Professor, New York University Center for the Prevention of Cardiovascular Disease NYU Langone Medical Center

Unmet Need

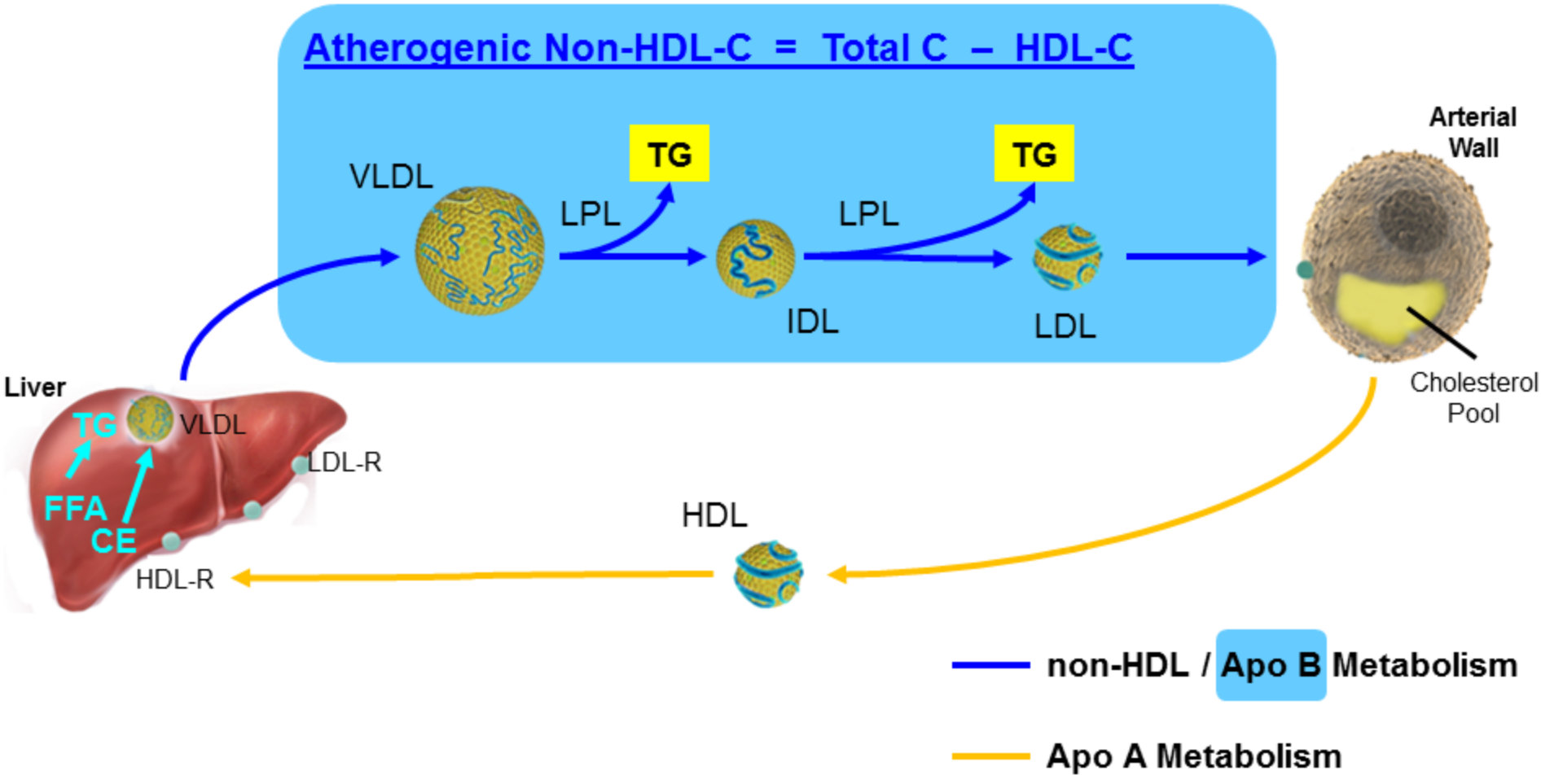
Michael Miller, MD
Director, Center for Preventive Cardiology
University of Maryland Medical Center

Non-HDL-C Reduction in Statin Treated Patients with Elevated TG

- Elevated non-HDL-C is a CHD risk factor
  - Even when LDL-C is within target range
- Reducing non-HDL-C is often addressed by lowering TG
  - Patients with TG > 200 mg/dL may be considered for TG-lowering therapy
    - Especially with underlying CV risk factors
- No prospective outcomes studies in statin-treated patients with TG > 200 mg/dL

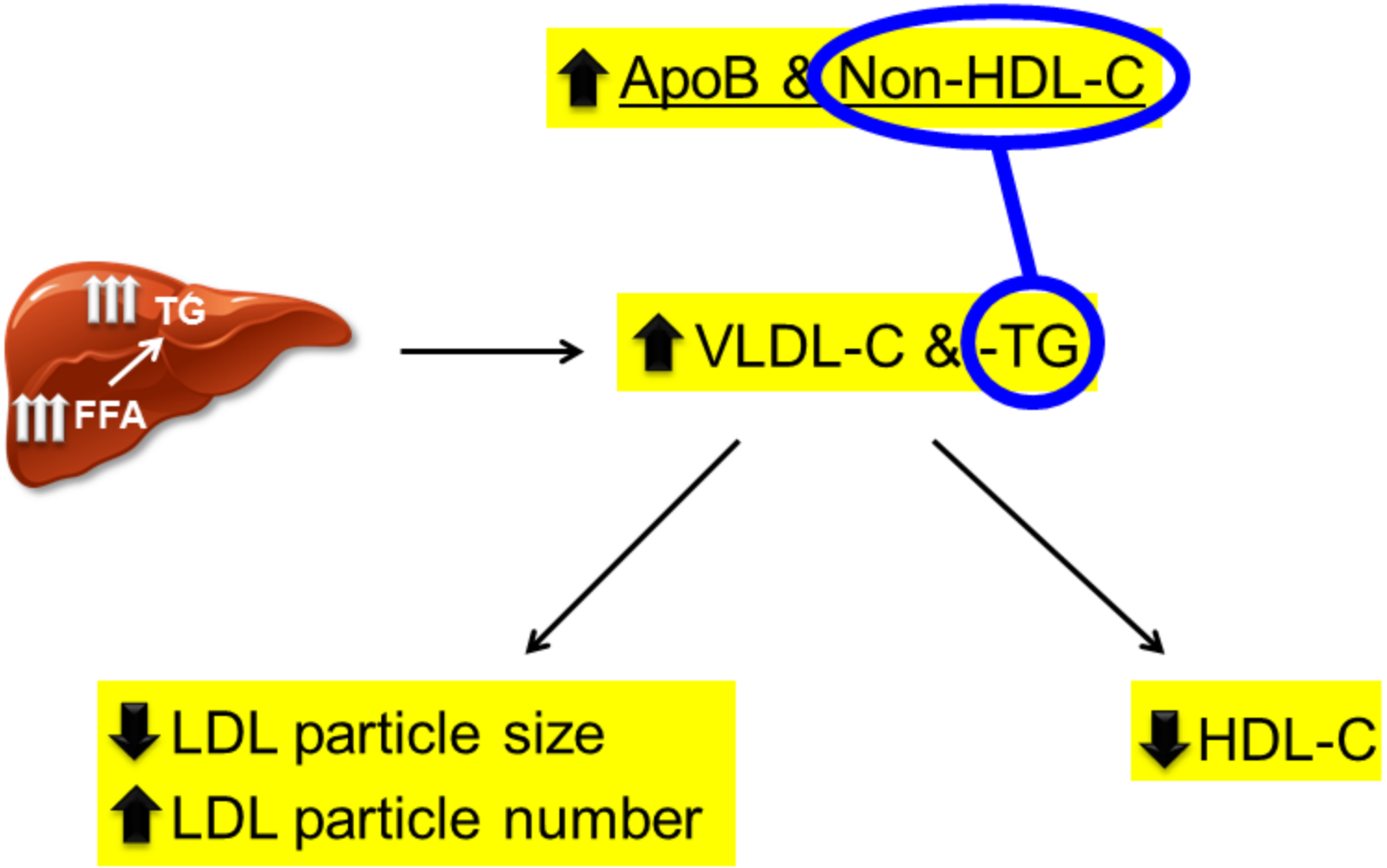
Varbo. *J Am Coll Cardiol* (2013)

Non-HDL-C Includes Cholesterol Carried by Atherogenic Lipoproteins



Adapted and updated from Brewer HB. *Am J Cardiol* (1999)

Untreated Hypertriglyceridemia Increases Potential Atherogenic Risk

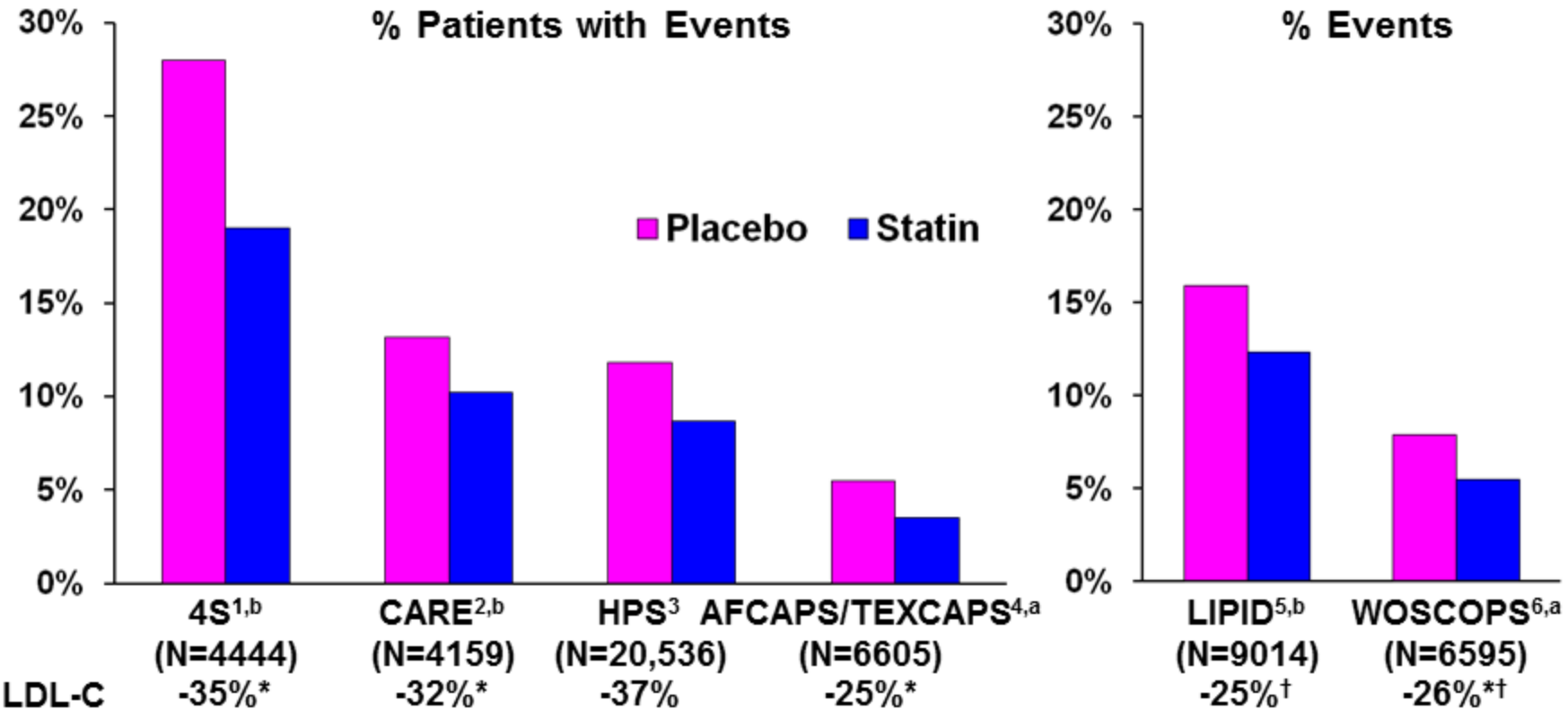


Rader DJ. *J Clin Invest* (2006)

Statins Partially Address Lipid Abnormalities in Mixed Dyslipidemia

- Statin Therapy
  - ↓ atherosclerotic lipids (LDL-C, TG, VLDL-C)
  - ↑ HDL-C
- Mixed dyslipidemia
  - Often in patients with established CHD or CV risk factors
  - Often presents with persistent TG elevations despite statin therapy

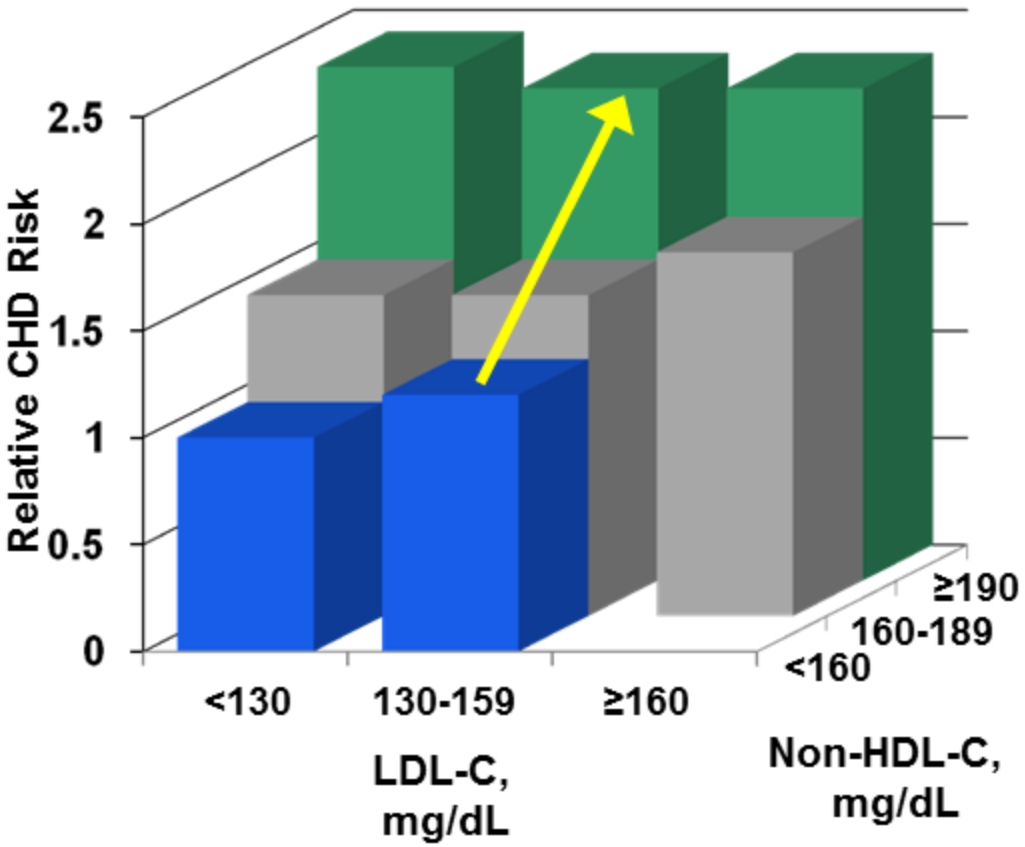
Patients Still Have CHD Risk Even when LDL-C Treated to Optimal Target



* Change from baseline; † Placebo-adjusted change from baseline;
a) Primary Prevention, b) Secondary Prevention
1) 4S Group (1994); 2) Sacks (1996); 3) HPS Group (2002); 4) Downs (1998); 5) LIPID Group (1998); 6) Shepherd (1995)

Framingham Heart Study Data Suggest that Non-HDL-C Predicts CHD Risk

- Non-HDL-C predicts CHD at all LDL-C levels
- LDL-C predictive value diminishes as non-HDL-C increases



Liu. *Am J Cardiol* (2006)

LDL-C, Non-HDL-C, & Apo B Linked to CV Risk

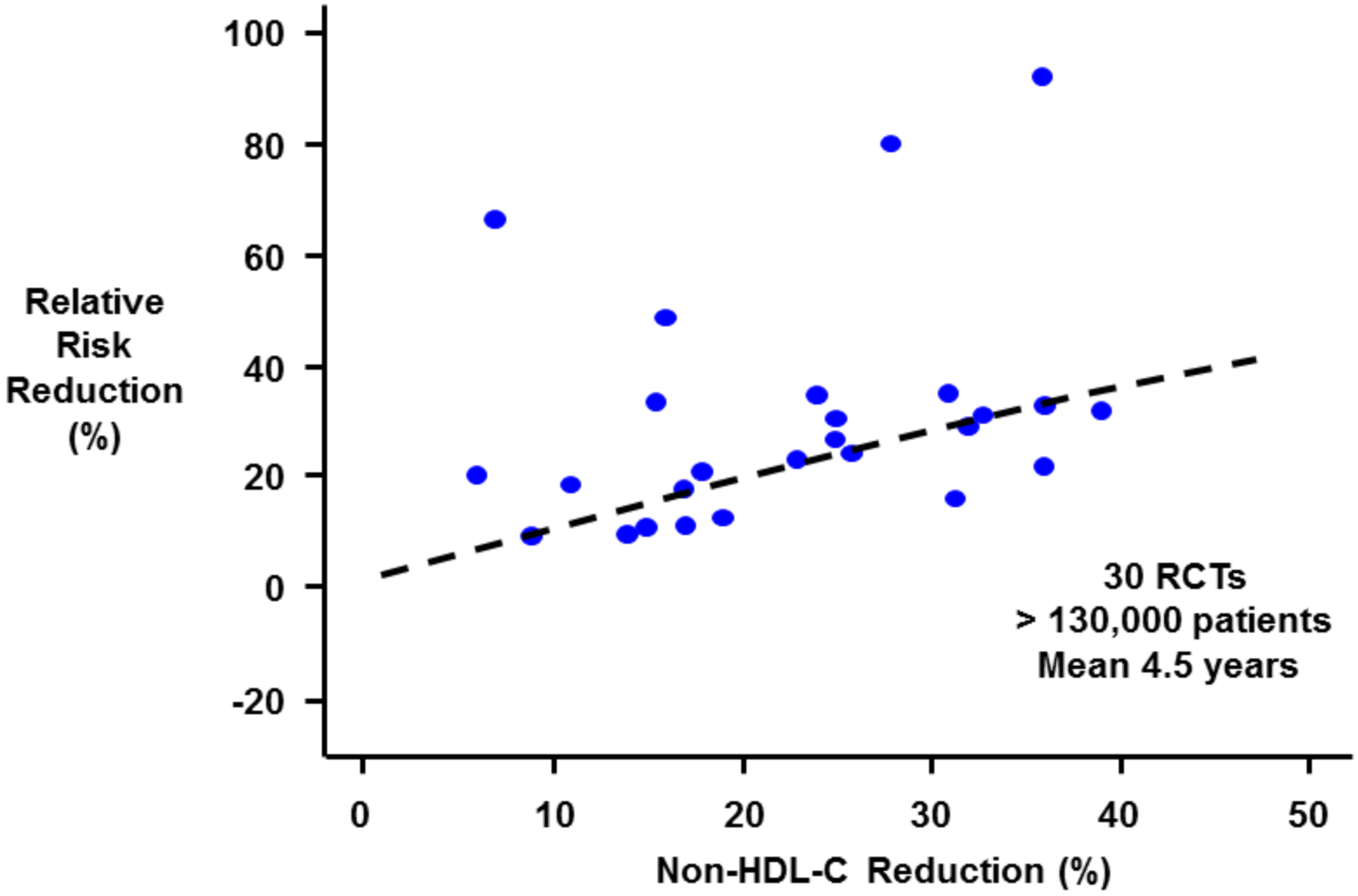
- Individual records, without initial vascular disease
  - >302,000 patients with 12,785 CHD events
  - Non-HDL-C calculated from all records
  - LDL-C & Apo B directly measured in >44,000 records

Biomarker	Per mg/dL Change	CHD Hazard Ratio (95% CI)
Non-HDL-C	**43**	**1.50 (1.39 - 1.61)**
LDL-C	**33**	**1.38 (1.09 - 1.73)**
Apo B	**29**	**1.58 (1.39 - 1.79)**

- Elevated TG levels commonly correlate with increased non-HDL lipoprotein

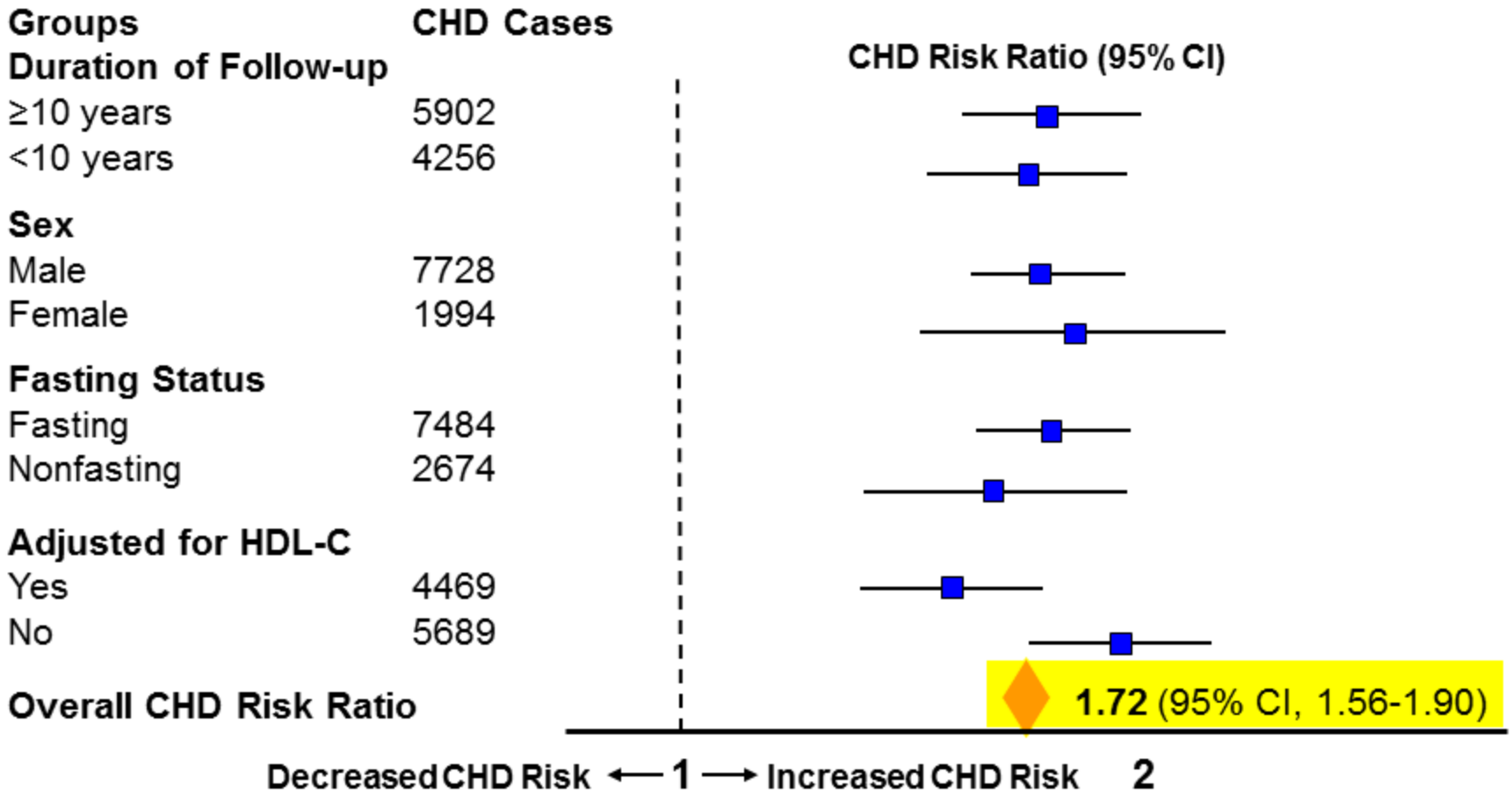
The Emerging Risk Factors Collaboration. *JAMA* (2009)

1:1 Relationship Between Non-HDL-C Reduction and CHD Event Risk Reduction



Adapted from Robinson JG. *JACC* (2009)

Meta-analysis of 29 Studies Shows that Elevated TG is CHD Risk Factor



N=262,525
Sarwar. *Circulation* (2007)

TG is an Interdependent Biomarker of CV Risk

Study	Patient Population	Interpretation of TG as Independent Risk
ERFC	No prior CVD	TG association with CV outcomes lost after adjusting for HDL-C & non-HDL-C
IDEAL & TNT Pooled analysis	Secondary prevention (CHD, ACS) on statin therapy	TG association with CV outcomes lost after adjusting for HDL-C & Apo B
PROVE-IT TIMI 22	ACS, on statin therapy with LDL-C at goal	TG independently associated with lower recurrence CHD risk even after adjustment for LDL-C or non-HDL-C

No Outcome Trials Exclusively in Statin-treated Patients with TG ≥ 200 mg/dL

- Outcome trials using TG-lowering therapies have not focused on patients with TG ≥ 200 mg/dL
- TG-lowering therapies utilized
  - Non-Omega-3 therapies
    - Fibrates
    - Niacin
  - Omega-3 therapies

Outcome Trials Utilizing Fibrates and Niacin Therapies Added to Statin

Trial Year Published	CV Risk Profile	Daily Intervention Added to Statin	Primary Endpoint	OR / HR (*p*-value)
ACCORD[1] 2010	Type II DM	Fenofibrate	MACE -8%	OR = 0.92 (0.32)
AIM-HIGH[2] 2011	CVD 2º Prevention	Niacin ER	Ext. MACE +2%	HR = 1.02 (0.79)
HPS2-THRIVE[3,4] 2013	CVD 2º Prevention	Niacin + Laropiprant	Major vascular events -4%	HR = 0.96 (0.29)

1) ACCORD Study Group. *N Engl J Med* (2010); 2) AIM-HIGH Investigators. *N Engl J Med* (2011); 3) HPS2-THRIVE Collaborative Group. *Euro Heart J* (2013); 4) HPS2-THRIVE. *ACC Meeting San Francisco, CA* (2013)

Non-Omega-3 Outcome Trials Lipid Parameters

Trial Year Published	Baseline LDL-C (mg/dL) (SD)†	Baseline non-HDL-C (mg/dL)	Baseline TG (mg/dL) (IQR)	TG Change (%)
ACCORD[1] 2010	101 (±31)	137*	162 (Median IQR: 113, 229)	-22%
AIM-HIGH[2] 2011	76 (±25)	112*	163 (Median IQR: 127, 218)	-31%
HPS2-THRIVE[3,4] 2013	63 (±17)	84*	108 (±73 Median IQR)	-33%

* Calculated from TC – HDL-C; SD for Non-HDL-C not available
† Mean ± SD unless otherwise stated

1) ACCORD Study Group. *N Engl J Med* (2010); 2) AIM-HIGH Investigators. *N Engl J Med* (2011); 3) HPS2-THRIVE Collaborative Group. *Euro Heart J* (2013); 4) HPS2-THRIVE. *ACC Meeting San Francisco, CA* (2013)

Outcome Trials Utilizing Omega-3 TG-lowering Therapies Added to Statin

Trial Year Published	CV Risk Profile	EPA+DHA Dose (g/day)	Patients on Statin	Primary Endpoint	HR / OR (*p*-value)
JELIS 2007	Hyper-cholesterolemic	1.8 (EPA only)	100%	Expanded MACE	HR = 0.81 (0.011)
GISSI-HF 2008	Symptomatic HF	0.85	~ 23%	Death ± CV hosp.	HR = 0.91 (0.041)
DOIT 2010	High CV risk	2	27%	All Cause Mortality (post-hoc)	HR = 0.53 (0.063)
Alpha-Omega 2010	History of MI	0.376	~ 87%	MACE	HR = 1.01 (0.93)
OMEGA 2010	Recent MI	0.84	~ 95%	Sudden Cardiac Death	OR = 0.95 (0.93)
SU.FOL.OM3 2010	Recent CHD or ischemic event	0.6	~ 87%	MACE	HR = 1.08 (0.64)
ORIGIN 2012	High CV event risk, dysglycemia	0.84	~ 54%	CV death	HR = 0.98 (0.72)
Risk & Prev. 2013	High CVD risk	0.84	41%	CV death / CV hospitalization	HR = 0.98 (0.58)

Highest value reported if multiple values listed (preceded by ~)

Omega-3 Outcome Trials
Lipid Parameters

Trial Year Published	Baseline LDL-C (mg/dL)	Baseline non-HDL-C (mg/dL)	Baseline TG (mg/dL)	TG Change
JELIS 2007	~ 182	~ 217	~ 154	- 9.0 v. - 4.0%
GISSI-HF 2008	~ 122	NR	126	- 7.1 mg/dL
DOIT 2010	158	190	151	- 15.1 to - 20.4 mg/dL
Alpha-Omega 2010	~ 102	~ 135	~ 150	- 7.1 v. + 4.4 mg/dL
OMEGA 2010	NR (EoS: 95)	NR	127	EoS: 121 v. 127 mg/dL
SU.FOL.OM3 2010	~ 104	~ 133	~ 115	NR
ORIGIN 2012	112	~ 144	~ 142	- 14.5 mg/dL
Risk & Prev. 2013	132	~ 165	150	- 28.2 v. - 20.1 mg/dL

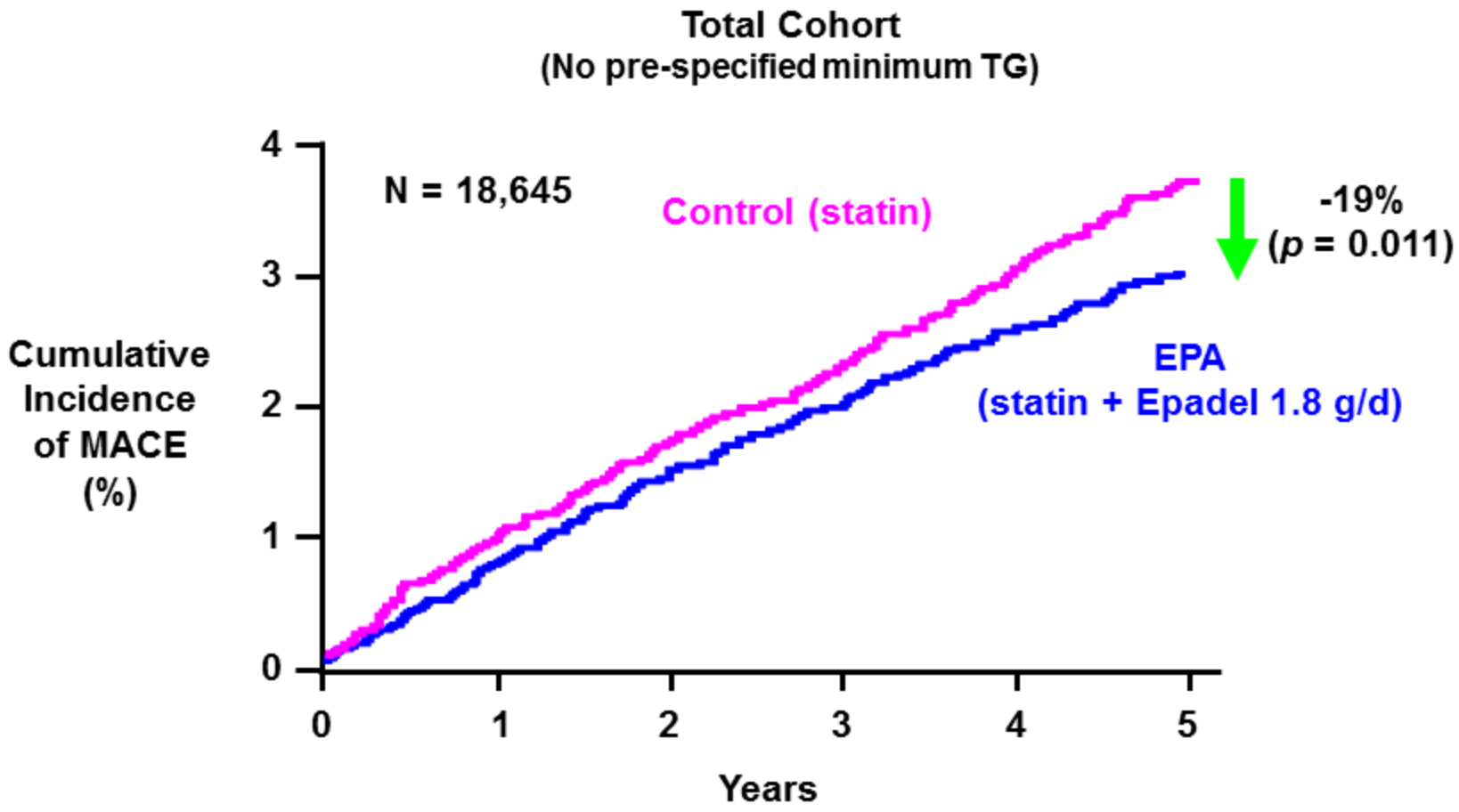
NR = Not Reported. Ranges not provided in publication. Highest value reported if multiple medians listed (preceded by ~)

Subgroup Analyses Suggests CV Benefit in Patients with Elevated TG

Trial (Drug + Statin)	Primary Endpoint: Full Trial (*p*-value)	Lipid Subgroup Criterion	Subgroup Endpoint (*p*-value)
ACCORD (Fenofibrate)	MACE -8% (0.32)	TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl	MACE -31% (0.0567)
AIM-HIGH (Niacin ER)	Ext. MACE +2% (0.79)	TG ≥ 200 mg/dl HDL-C < 32 mg/dl	Ext. MACE -36% (0.032)
HPS2-THRIVE (Niacin ER + laropiprant)	Major vascular events -4% (0.29)	TG ≥ 151 mg/dl* HDL-C < 35 mg/dl*	Major vascular events 0% (0.95)
JELIS (ethyl EPA)	Coronary events -19% (0.011)	TG ≥ 150 mg/dl HDL-C ≤ 40 mg/dl	Coronary events -53% (0.043)

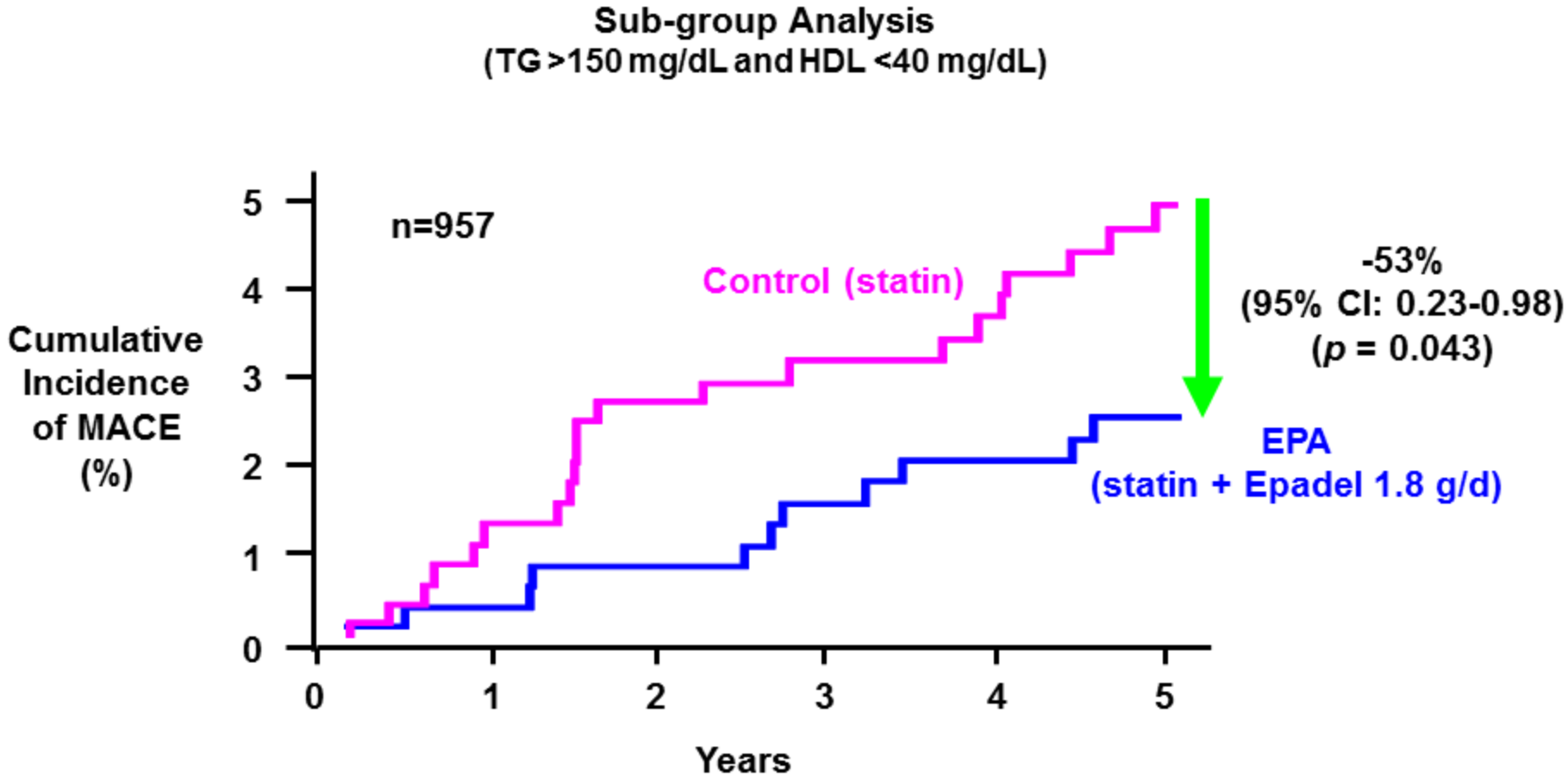
* Study not published, subgroup criterion based on materials presented publicly by investigator(s)

EPA Benefit on CHD Risk Suggested by JELIS Trial



p-value adjusted for age, gender, smoking, diabetes, and hypertension
Yokoyama. *Lancet* (2007)

Mixed Dyslipidemia Subgroup Analysis in JELIS Trial



p-value adjusted for age, gender, smoking, diabetes, and hypertension.
Saito. *Atherosclerosis* (2008)

Appropriate Studies Needed in Hypertriglyceridemia Patients

- Inconsistent TG-lowering outcome trial results in patients with median TG below 200 mg/dL
- No study has specifically enrolled statin-treated patients with CVD risk and median TG ≥ 200 mg/dL
- Subgroup analyses of statin-treated patients with elevated TG suggest CV benefit from TG-lowering therapy

Unmet Need for Mixed Dyslipidemia Patients with High TG at LDL-C Goal

- Despite statin therapy, CHD risk remains
  - TG-lowering therapies often used to reduce non-HDL-C in patients with persistent TG elevations (200 to <500 mg/dL)
- Products that can be combined with statin
  - No adverse effect on LDL-C

ANCHOR Efficacy

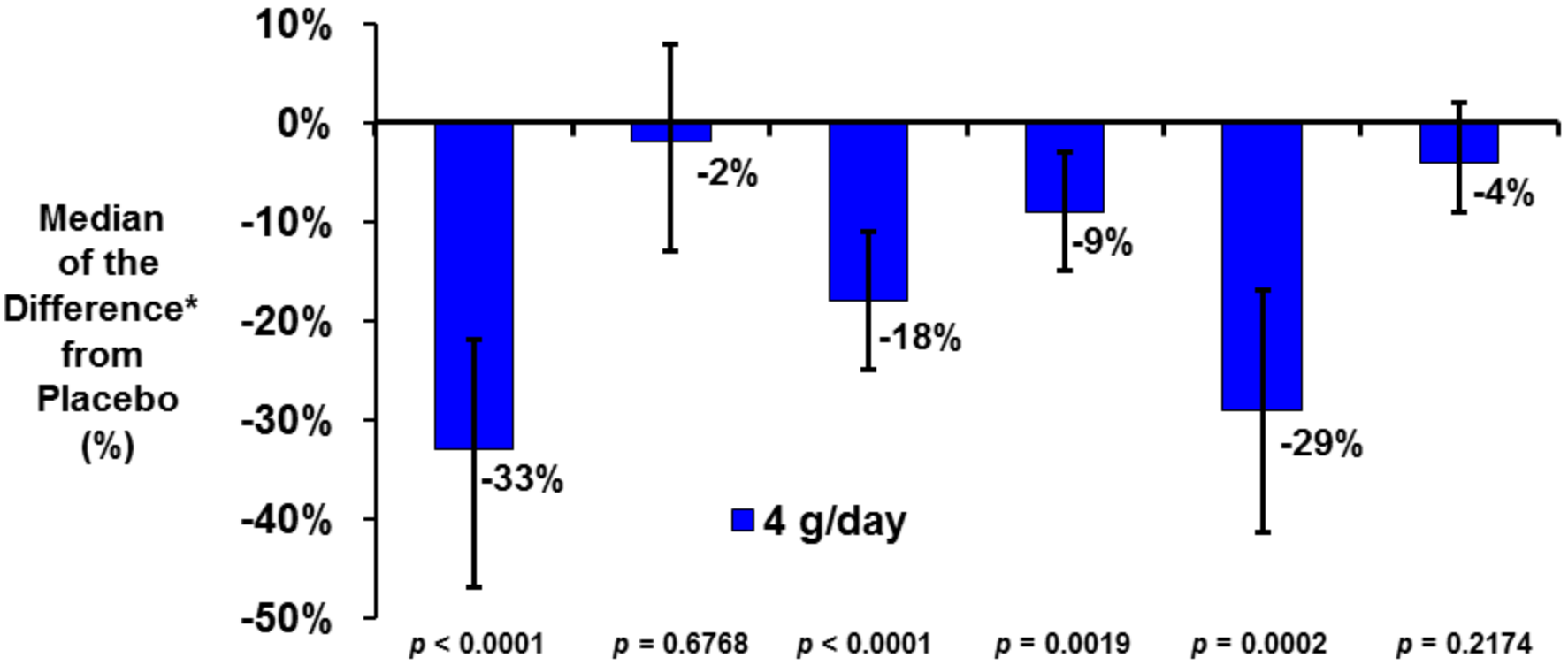
Declan Doogan, MD
Chief Medical Officer
Amarin Pharma, Inc.

ANCHOR Studied Vascepa in Mixed Dyslipidemia Patients at High CHD Risk

- Designed under a SPA agreement
- Determine TG reduction in patients on optimized statin therapy for LDL-C control
  - Achieve 6 percentage point non-inferiority margin for LDL-C
- Determine improvement in biomarkers of CV disease

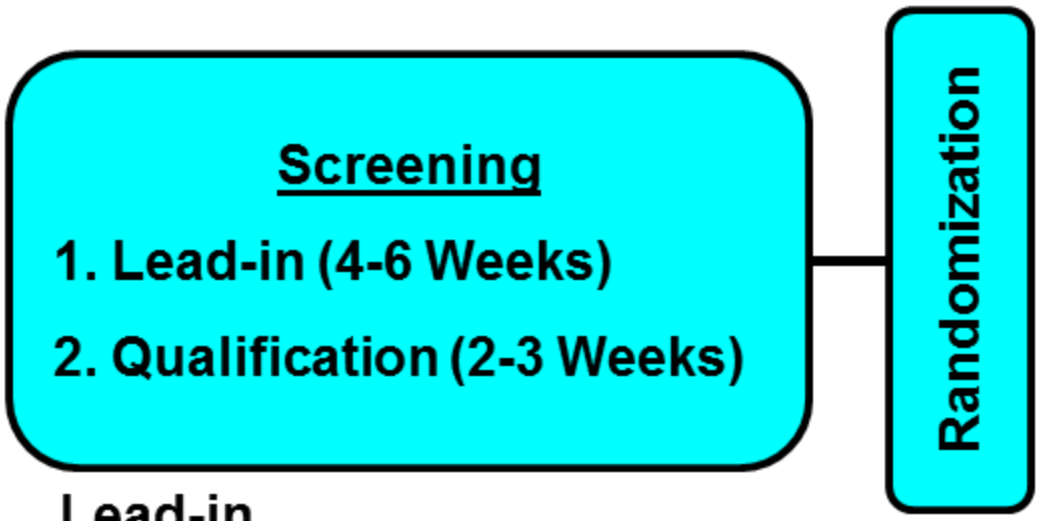
MARINE Study Demonstrated Efficacy in Severe Hypertriglyceridemia

	TG	LDL-C	Non-HDL-C	Apo B	VLDL-C	HDL-C
4 g/day	N=76	N=76	N=76	N=75	N=76	N=76
Baseline mg/dL	680	91	225	121	123	27
Week 12 mg/dL	502	86	206	117	104	26



Bays. *AJC* (2011); Hodges-Lehmann median estimate; *p*-values compared to placebo

ANCHOR was 12-week, Randomized, Placebo-controlled Study in US



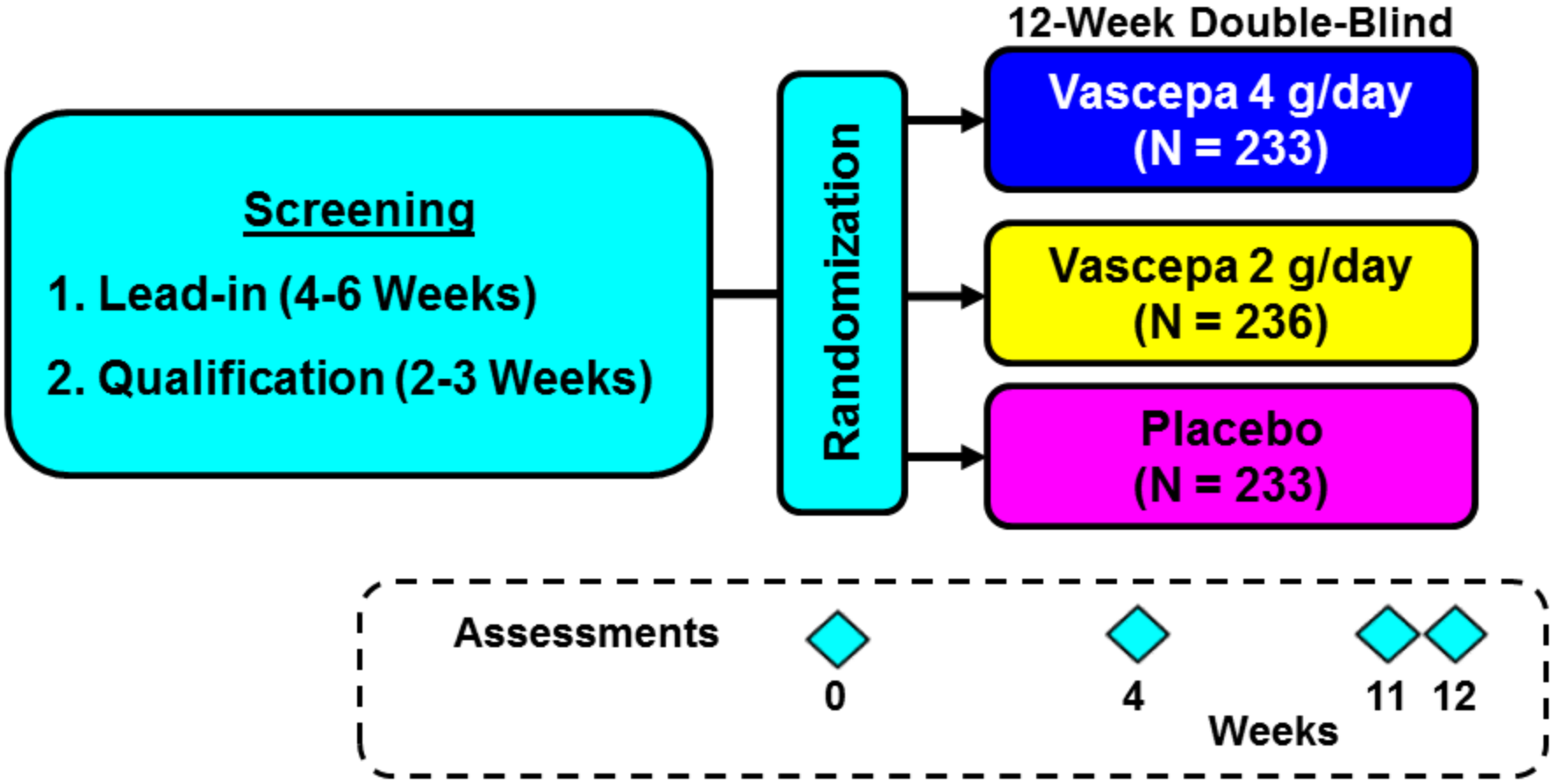
Lead-in

- Counseling on diet and lifestyle
- Initiation and/or adjustment of statin (if needed)
- Wash-out of non-statin lipid lowering medications

Qualification

- LDL-C treated to goal (<100 mg/dL)
- Stable statin dose for ≥ 4 weeks
- TG and LDL-C values based on average of 2 visits

ANCHOR was 12-week, Randomized, Placebo-controlled Study in US



ANCHOR Enrolled Dyslipidemic Adults with High CHD Risk at LDL-C Goal

- CHD or at High risk for CHD[1]
  - >20% risk of event in 10 years

	Entry Thresholds	Amendment
TG	≥ 200; < 500 mg/dL	≥ 185; < 500 mg/dL
LDL-C	≥ 40; ≤ 100 mg/dL	≥ 40; ≤ 115 mg/dL
Non-HDL-C	≥ 100 mg/dL	≥ 100 mg/dL
$HbA1_c$	≤ 9.0%	≤ 9.5%

[1] Grundy. (ATP-III) *Circulation* (2004)

ANCHOR Evaluated Lipid and Vascular Inflammation Endpoints

- Primary
  - Fasting TG
  - LDL-C non-inferiority
- Secondary
  - Non-HDL-C
  - VLDL-C
  - Lp-PLA_2
  - Apo B
- Exploratory, including HDL-C and hsCRP

Light Mineral Oil Used as Placebo

- Color and physical properties similar to Vascepa
- Publications support that mineral oil has little to no effect on lipids

Statistical Procedure

- Superiority test for TG
  - >90% power to detect a 15 percentage point treatment effect* (α=0.05)
- Non-inferiority (NI) test for LDL-C
  - 80% power to demonstrate 6 percentage point NI margin (95% CI, upper level)
- Step-down testing of 4g before testing 2g
- Sample size of 194 completers per group
- Stratification: type of statin, diabetes, gender

* Difference in % change from baseline, active versus placebo

Analysis Set

- Primary Analysis Set (PAS): randomized patients that received first dose and had a valid post-dose evaluation
  - Primary and secondary endpoints
- 15 randomized patients excluded from PAS
  - 7 in 4 g/day
  - 2 in 2 g/day
  - 6 in placebo

ANCHOR Baseline Characteristics were Similar Across Arms

Characteristic	Vascepa 4 g/day (N=233)	Vascepa 2 g/day (N=236)	Placebo (N=233)
Age (mean), y (range)	61 (31 – 85)	62 (31 – 84)	61 (36 – 88)
Age ≥ 65	39%	40%	37%
Male	61%	61%	62%
Caucasian	97%	96%	96%
Hispanic	12%	11%	13%
Weight (mean), kg	95	96	97
BMI (mean), kg/m^2	33	33	33
Hypertension	83%	83%	84%
Diabetes	73%	73%	73%

Summary of Diabetes and Cardiovascular Disease

Patients Characteristics (%)	Vascepa 4 g/day (N=226)	Vascepa 2 g/day (N=234)	Placebo (N=227)
With history of CVD	40%	42%	45%
History of Diabetes	73%	73%	73%
With history of CVD	19%	21%	23%
No CVD	54%	52%	50%
No history of diabetes	27%	27%	27%

ANCHOR Baseline Lipids were Similar Across Treatment Arms

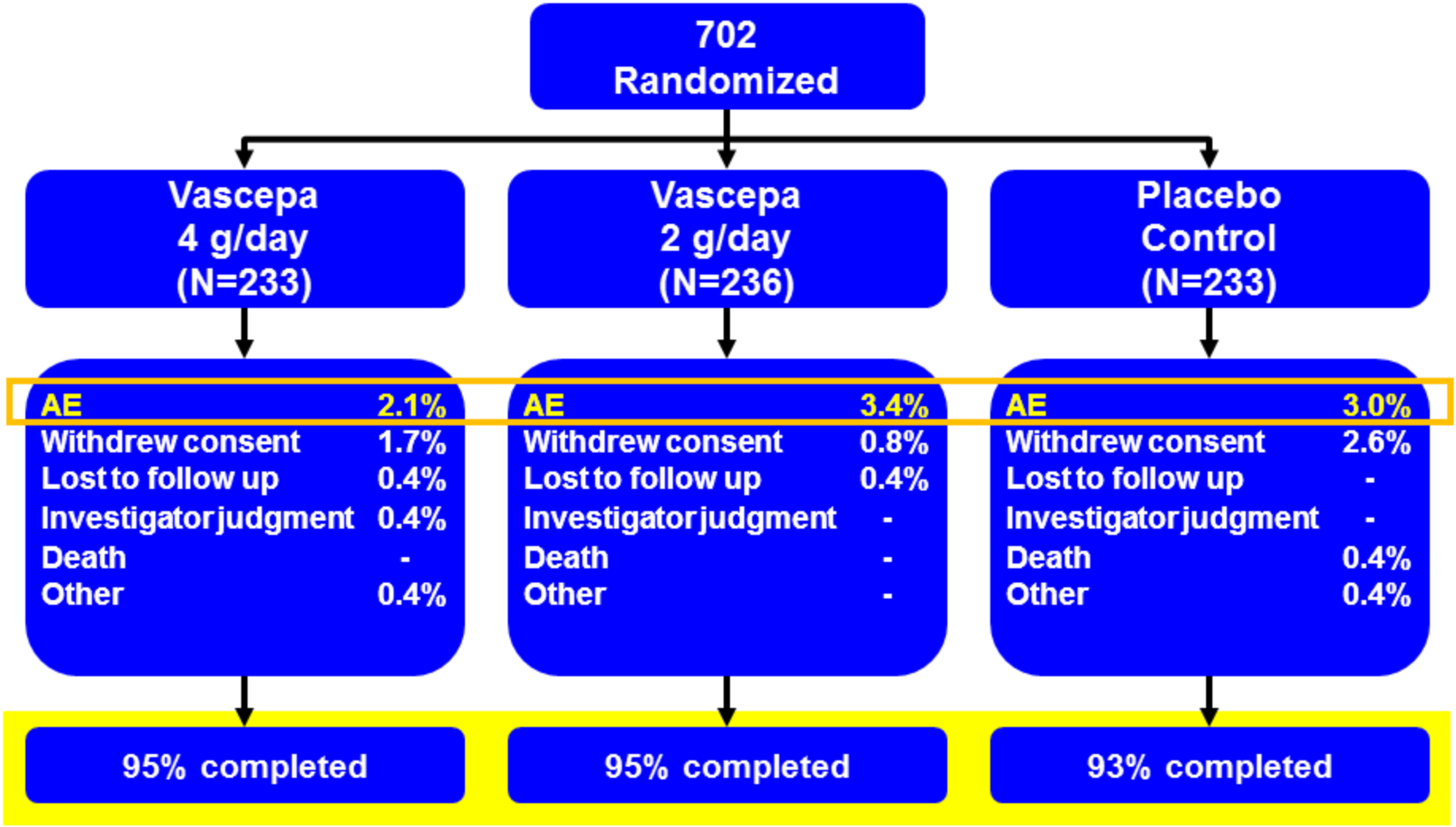
Baseline Characteristic Median (mg/dL)	Vascepa 4 g/day (N=233)	Vascepa 2 g/day (N=236)	Placebo (N=233)
TG	265	254	259
LDL-C	82	82	84
Non-HDL-C	128	128	128

Most Patients Treated with Medium or High Statin Efficacy Regimen

Statin Efficacy (%)	Vascepa 4 g/day (N=233)	Vascepa 2 g/day (N=236)	Placebo (N=233)
Lower[1]	7	7	6
Medium[2]	64	63	62
Higher[3]	30	30	32

1. Defined as simvastatin 5-10 mg
2. Defined as rosuvastatin 5-10 mg, atorvastatin 10-20 mg, simvastatin 20-40 mg, or simvastatin 10-20 mg + ezetimibe 5-10 mg
3. Defined as rosuvastatin 20-40 mg, atorvastatin 40-80 mg, simvastatin 80 mg, or simvastatin 40-80 mg + ezetimibe 5-10 mg

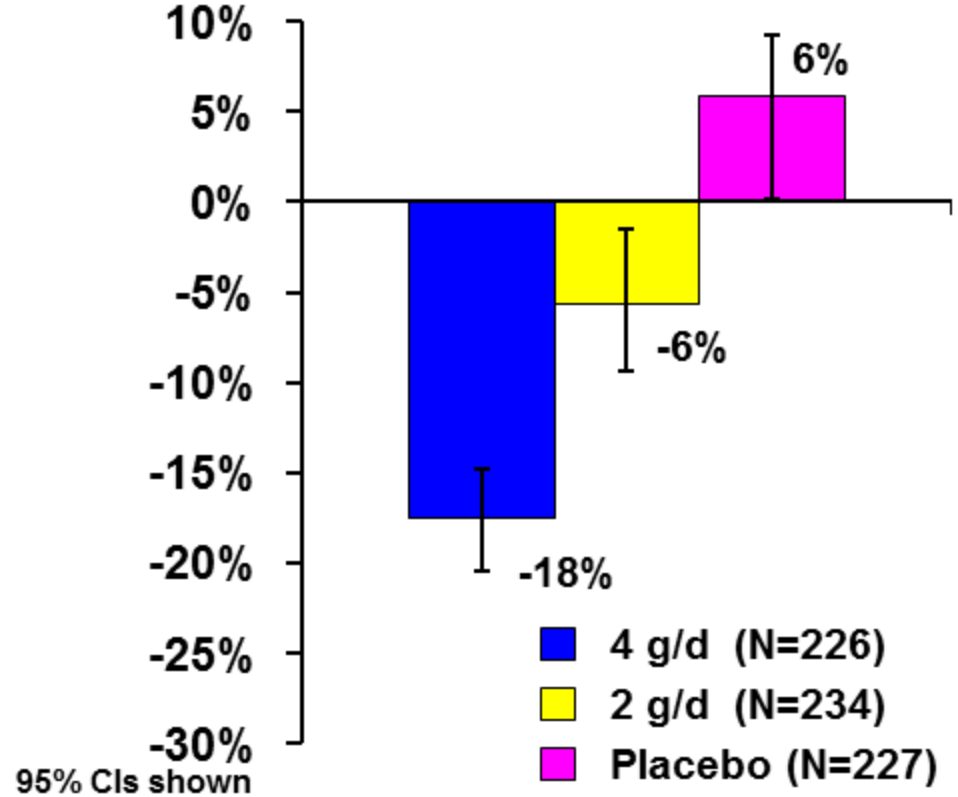
Disposition of Patients



Vascepa Significantly Improves TG Levels in Patients on Statins

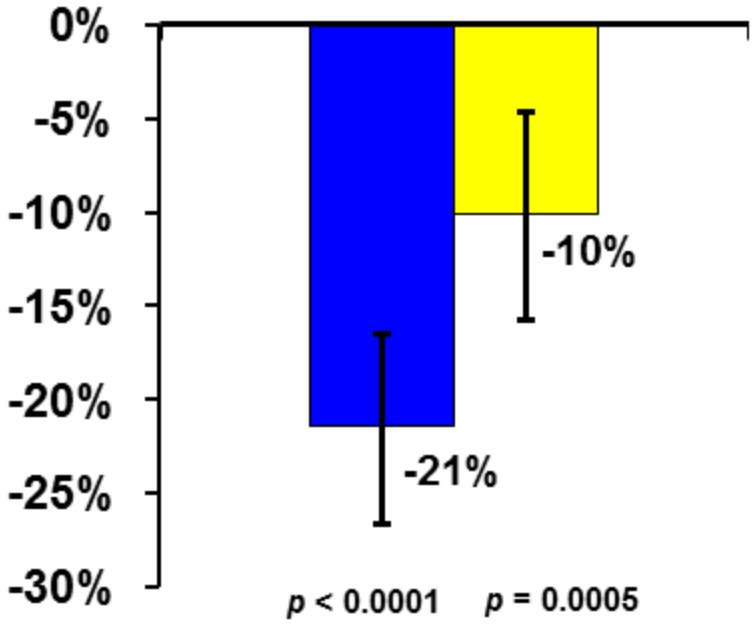
Median % Change from Baseline TG

Baseline mg/dL	265	254	259
Week 12 mg/dL	221	244	270



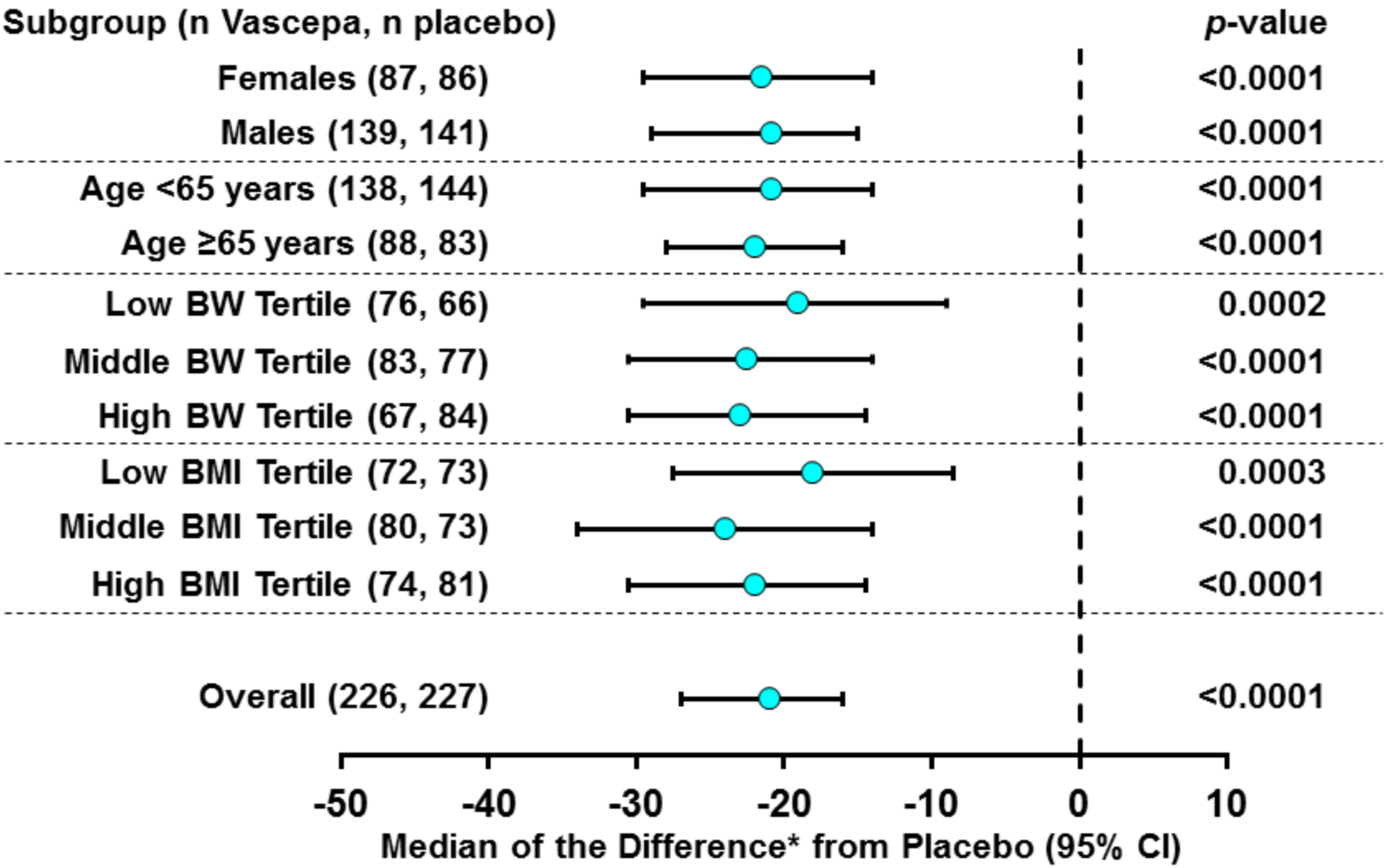
95% CIs shown
p-values compared to placebo

Median of the Difference* from Placebo



* Hodges-Lehmann median % point estimate of difference

Consistent Vascepa 4 g/day Reduction in TG by Subgroups

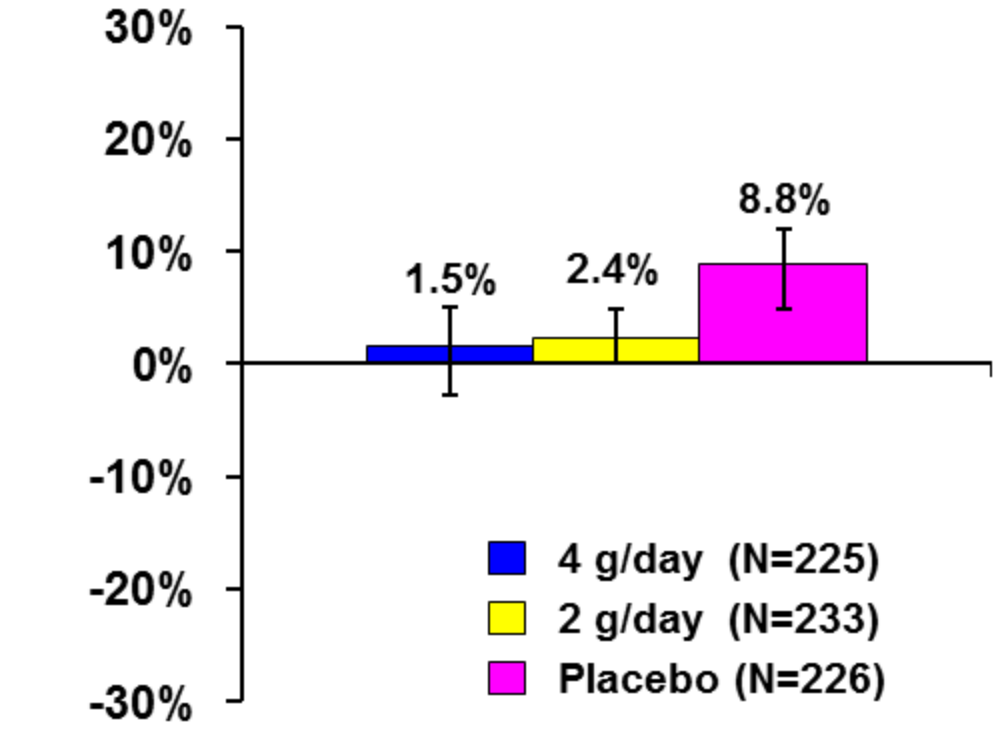


* Hodges-Lehmann median % point estimate of difference

Vascepa Demonstrated Non-inferiority for LDL-C when on Statins

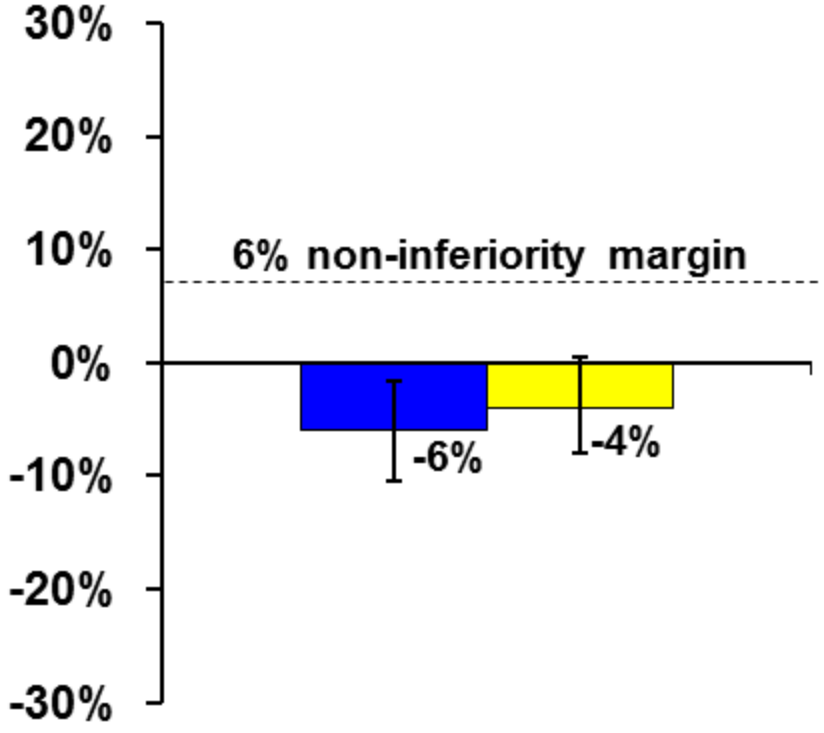
Median % Change from Baseline LDL-C

Baseline mg/dL	82	82	84
Week 12 mg/dL	83	87	89



95% CIs shown

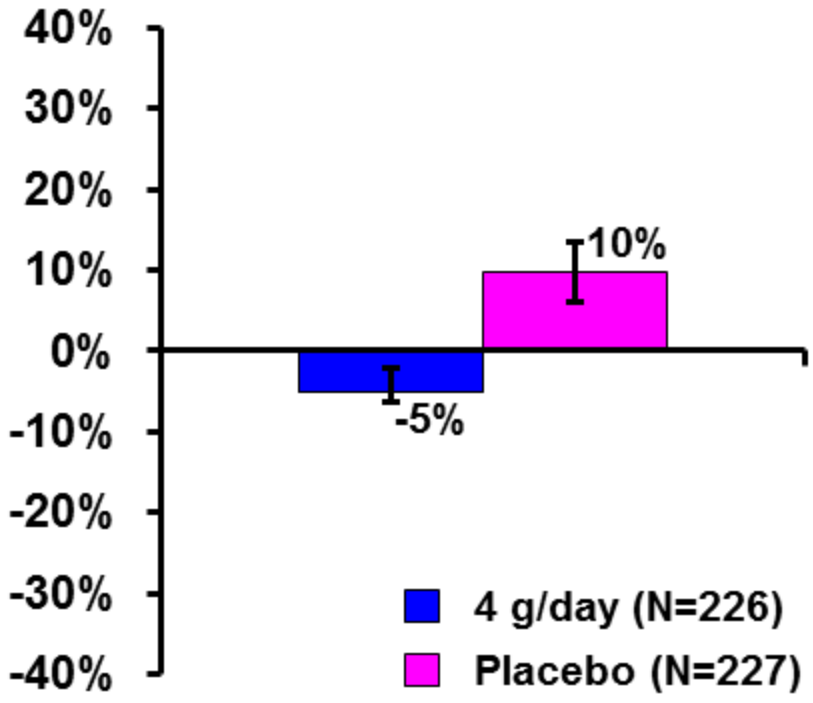
Median of the Difference* from Placebo



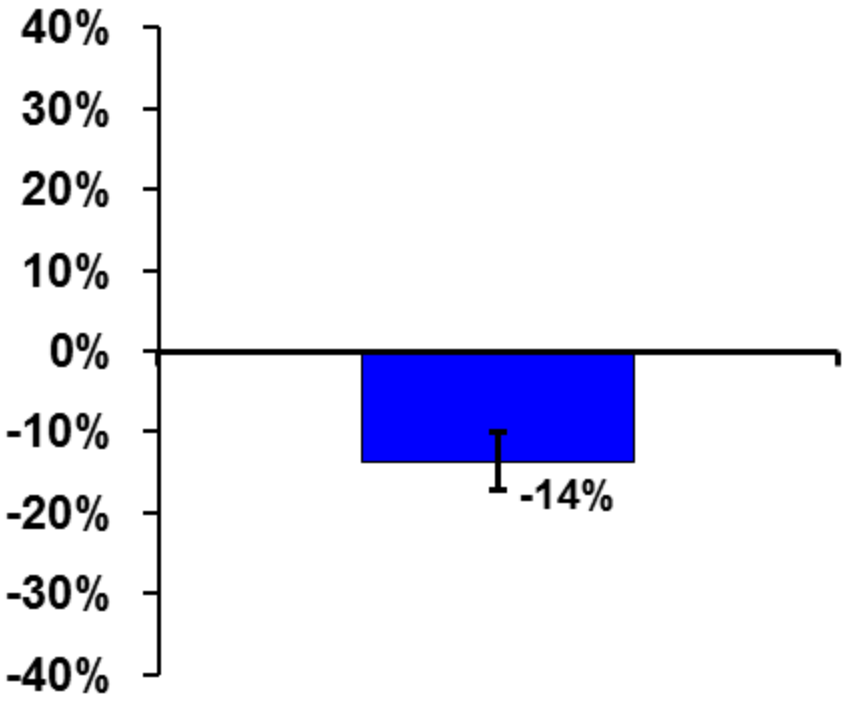
* Hodges-Lehmann median % point estimate of difference

Vascepa Significantly Improves Non-HDL-C Levels in Patients on Statins

	Median % Change from Baseline Non-HDL-C	
Baseline mg/dL	128	128
Week 12 mg/dL	122	138



Median of the Difference* from Placebo Non-HDL-C



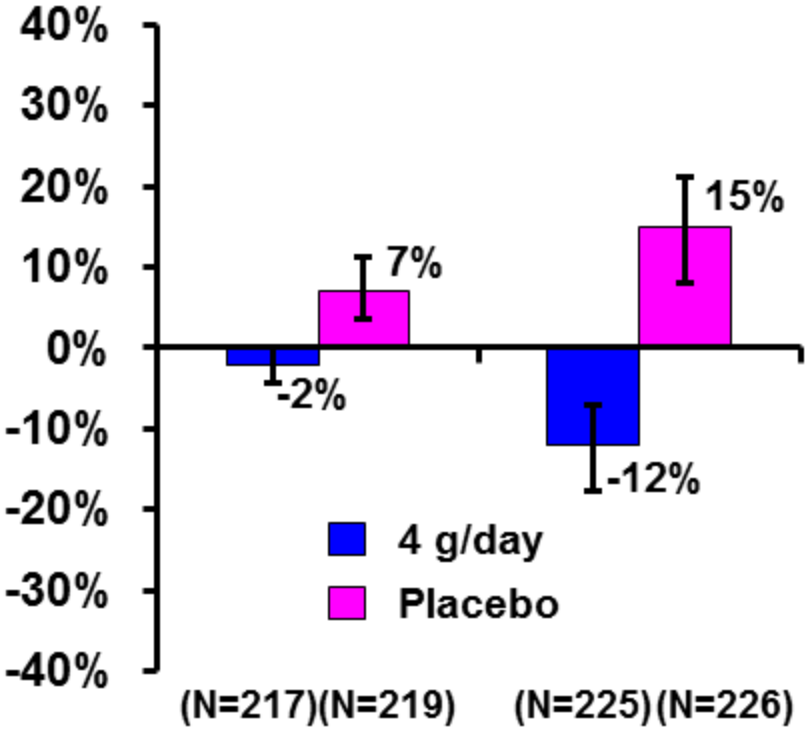
95% CIs shown
p-value compared to placebo

$p < 0.0001$

* Hodges-Lehmann median % point estimate of difference

Vascepa Consistently Improves Atherosclerosis Lipid Markers

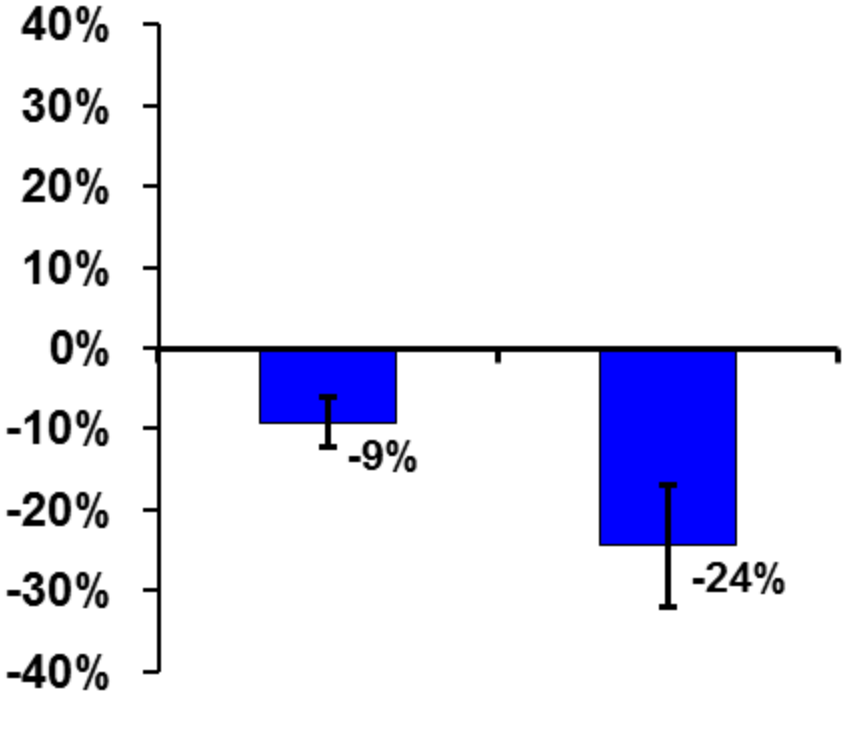
	Median % Change from Baseline			
	Apo B		VLDL-C	
Baseline mg/dL	93	91	44	42
Week 12 mg/dL	90	98	38	49



95% CIs shown
p-values compared to placebo

Median of the Difference* from Placebo

Apo-B	VLDL-C

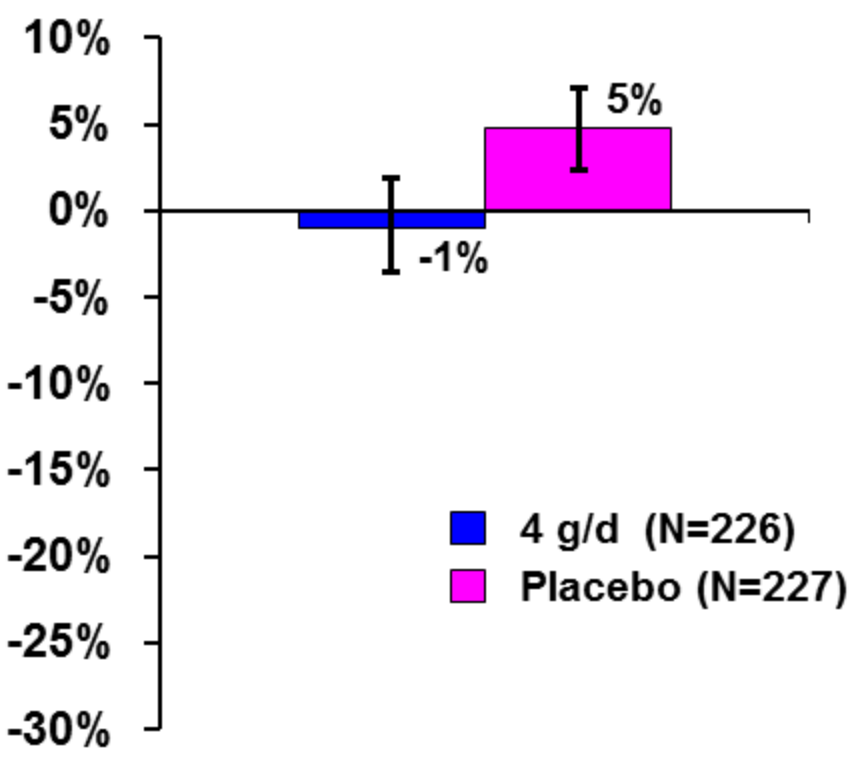


* Hodges-Lehmann median % point estimate of difference

Vascepa Effect on HDL-C

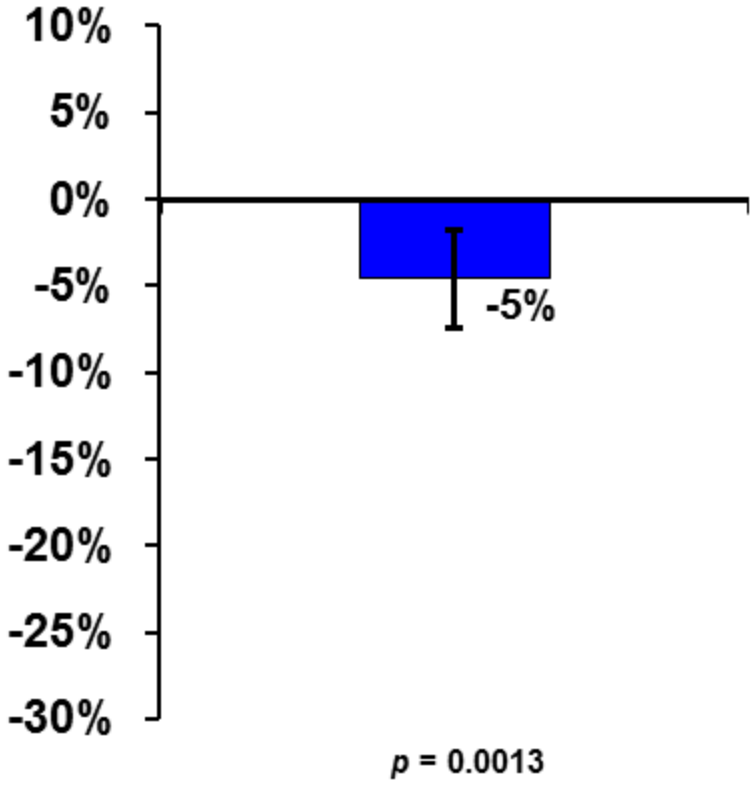
Median % Change from Baseline HDL-C

Baseline mg/dL	37	39
Week 12 mg/dL	37	40



p-value compared to placebo; 95% CIs shown

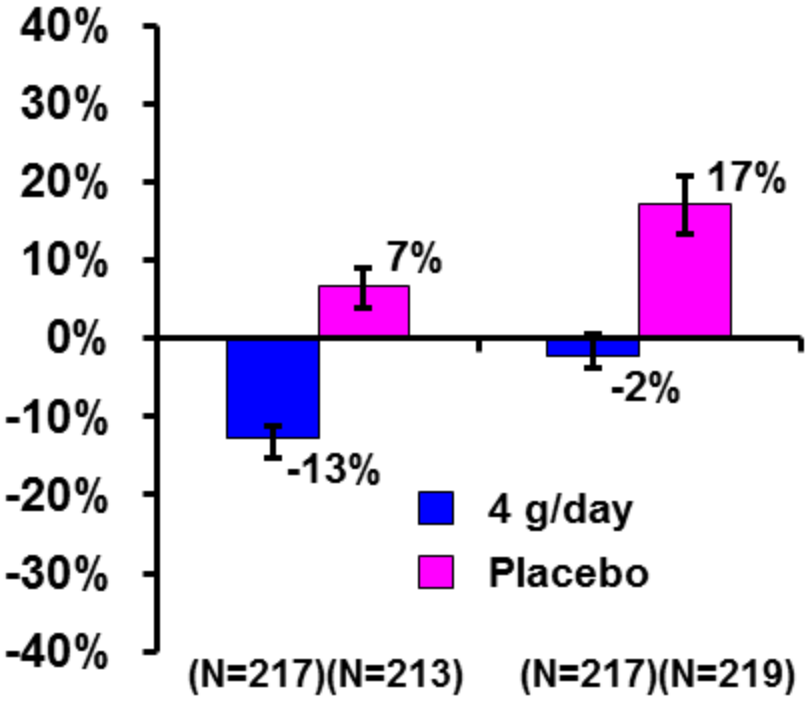
Median of the Difference* from Placebo



* Hodges-Lehmann median % point estimate of difference

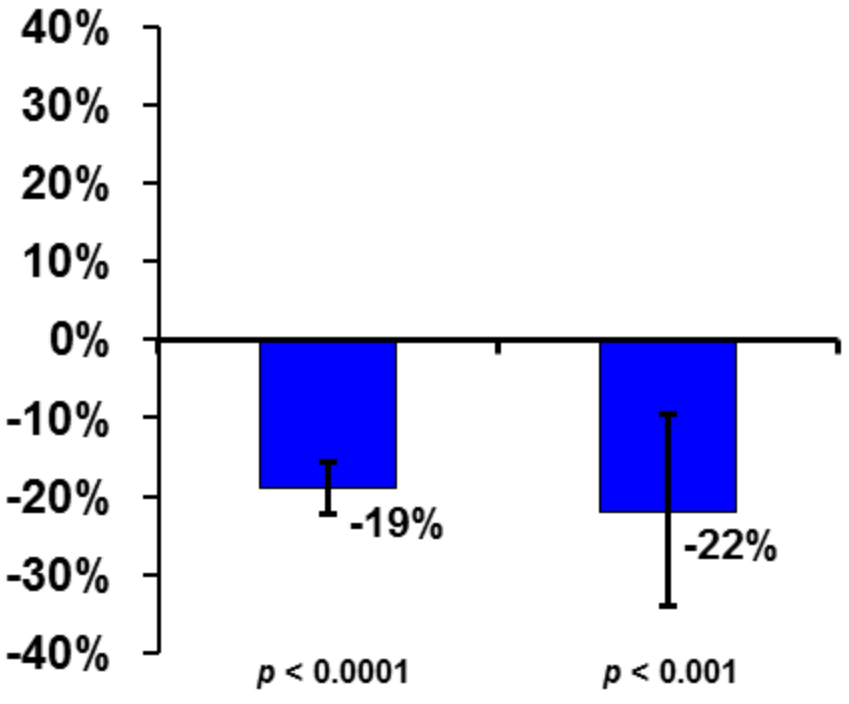
Vascepa 4 g/day Reduced Inflammatory Markers

	Median % Change from Baseline			
	Lp-PLA$_2$ ng/mL		hsCRP mg/L	
Baseline	180	185	2.2	2.2
Week 12	160	200	2.0	2.6



Median of the Difference* from Placebo

Lp-PLA$_2$ hsCRP

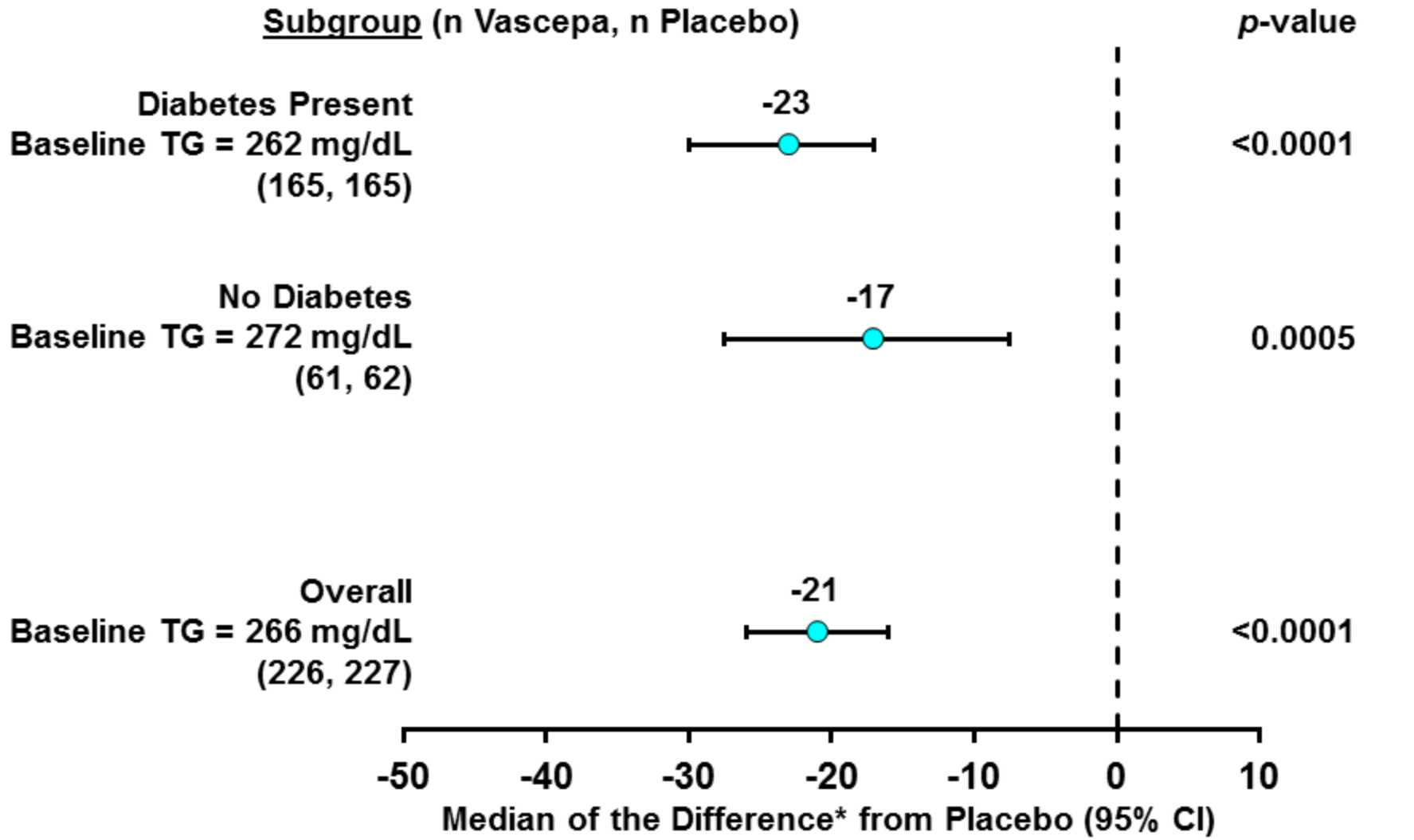


95% CIs shown

p-values compared to placebo

* Hodges-Lehmann median % point estimate of difference

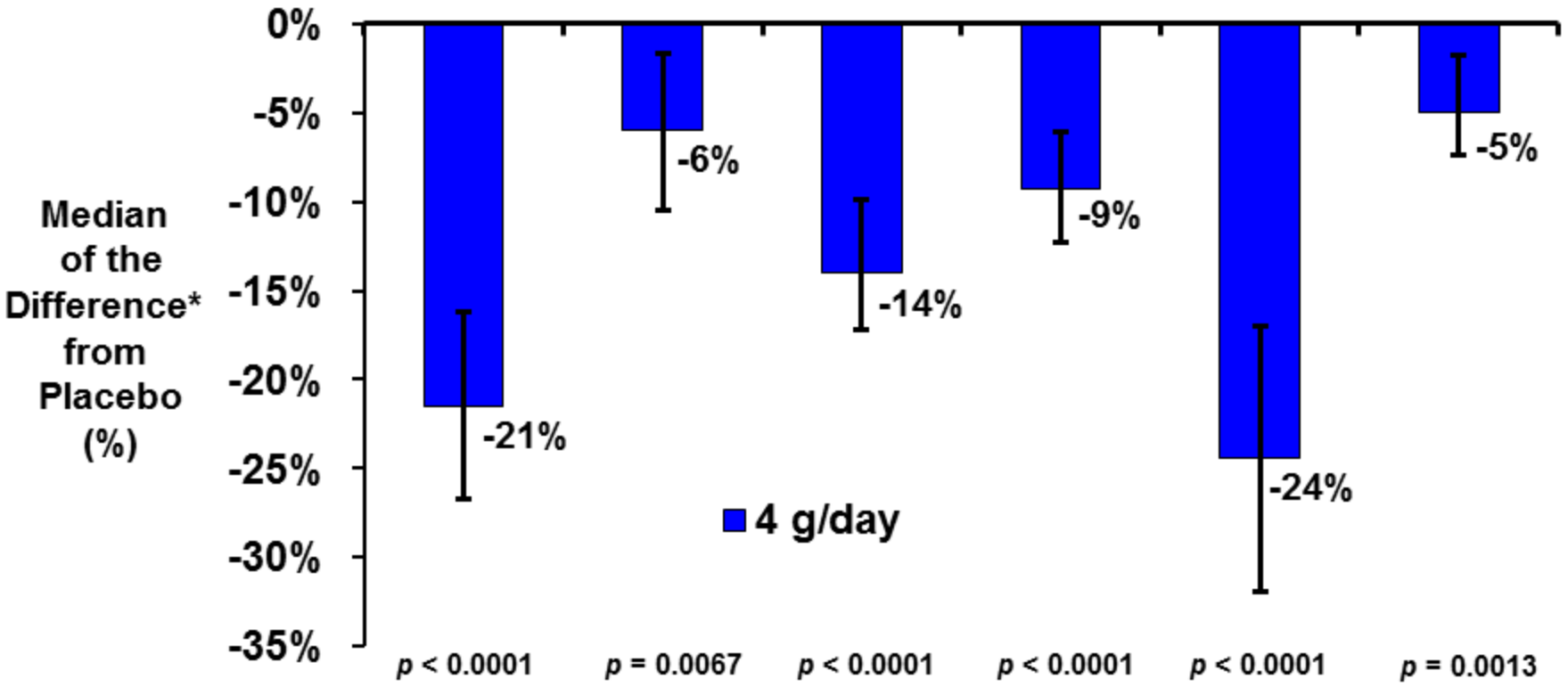
Vascepa 4 g/day Reduced TG in Patients with and without Diabetes



* Hodges-Lehmann median % point estimate of difference

Vascepa Add-on Therapy Demonstrated Efficacy in High Risk Patients

	TG	LDL-C	Non-HDL-C	Apo B	VLDL-C	HDL-C
4 g/day	N=226	N=225	N=226	N=217	N=225	N=226
Baseline mg/dL	265	82	128	93	44	37
Week 12 mg/dL	221	83	122	90	38	37



p-values compared to placebo; 95% CIs shown; * Hodges-Lehmann median % point estimate of difference

Vascepa Safety
ANCHOR Study Data

Steven Ketchum, PhD

President of Research and Development

Amarin Pharma

Safety Experience with Vascepa

- Current approved Vascepa label is based on integrated safety data from the MARINE and ANCHOR Studies
- Focus will be on ANCHOR safety population
  - Vascepa 4 g/day (recommended dose) and 2 g/day will be presented
- Post-marketing safety experience consistent with clinical trial results

ANCHOR AEs for Vascepa (4 g/day Group ≥ 2%)

ANCHOR Study Preferred Term (%)	Double-blind Treatment		
	4 g/day (N=233)	2 g/day (N=236)	Placebo (N=233)
Total AEs	45.5	44.9	48.1
Diarrhea	3.4	3.8	4.3
Urinary tract infection	2.6	1.3	2.6
Upper respiratory tract infection	2.6	1.3	2.1
Nausea	2.1	2.1	3.0
AE leading to discontinuation	2.1	3.4	5.2

ANCHOR Showed Low Rate of SAEs

ANCHOR Study SAE's by Category (%)	Double-blind Treatment 4 g/day (N=233)	2 g/day (N=236)	Placebo (N=233)
Total SAEs	3.0	2.5	2.1
General Disorders (non-cardiac chest pain)	0.9	0.8	0
Cardiac Disorders	0.4	0.8	0.9
Nervous System Disorders	0.9	0.4	0.4
Death	0	0	0.4

Adverse Events of Interest

- Bleeding AEs
- Hepatic lab value abnormalities
- Glucose control

ANCHOR
Bleeding-related Adverse Events

Preferred Bleeding Term (%)	Double-blind Treatment 4 g/day (N=233)	2 g/day (N=236)	Placebo (N=233)
Total Subjects with Bleeding-related AE's	2.6	3.0	1.7
Total of Bleeding-related AEs	2.6	3.8	1.7
Anemia	0.9	0.4	0
Spontaneous hematoma	0	0.4	0
Hematochezia	0.4	0	0.4
Contusion	0	0.8	0.9
Hematoma	0	0.4	0
Infusion Site Hematoma	0	0	0.4
Subarachnoid Hemorrhage	0.4	0.4	0
Subdural Hematoma	0	0.4	0
Traumatic Hematoma	0.9	0.4	0
Uterine Hemorrhage	0	0.4	0

All patients with bleeding event were taking anti-platelet or anti-coagulant therapy

ANCHOR
Hepatic Laboratory Values

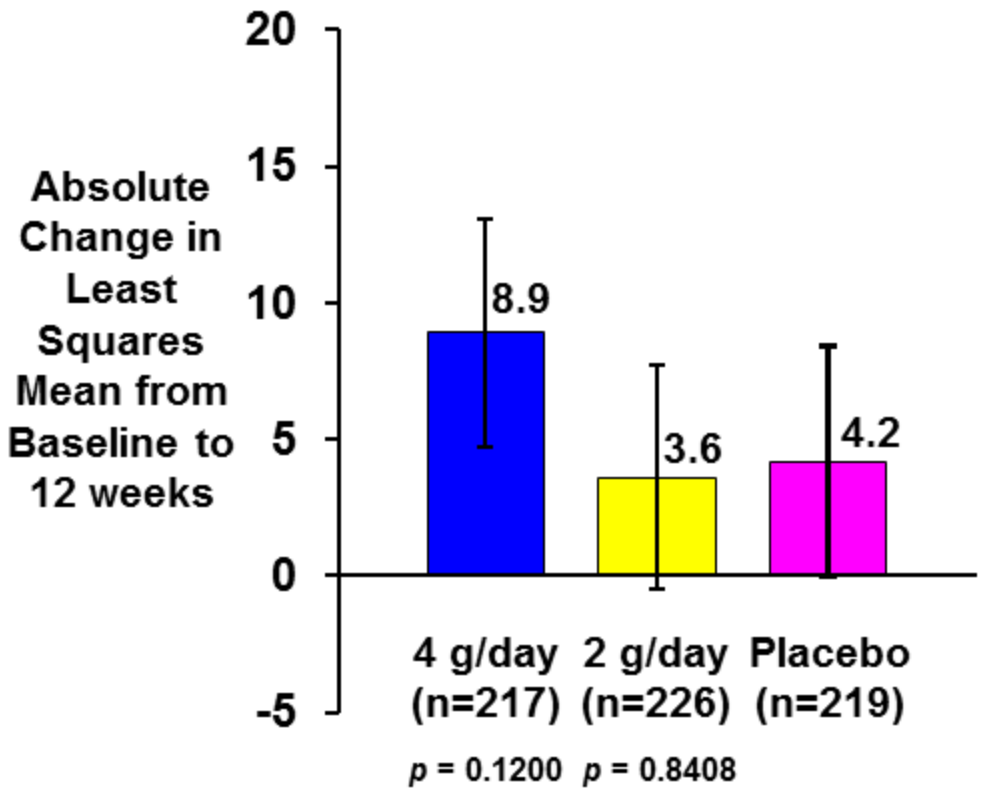
- ALT and AST > 3ULN
  - 2 patients Vascepa 4 g/day
  - 1 patient placebo
- CK > 5ULN
  - 1 patient Vascepa 2 g/day
  - 1 patient placebo

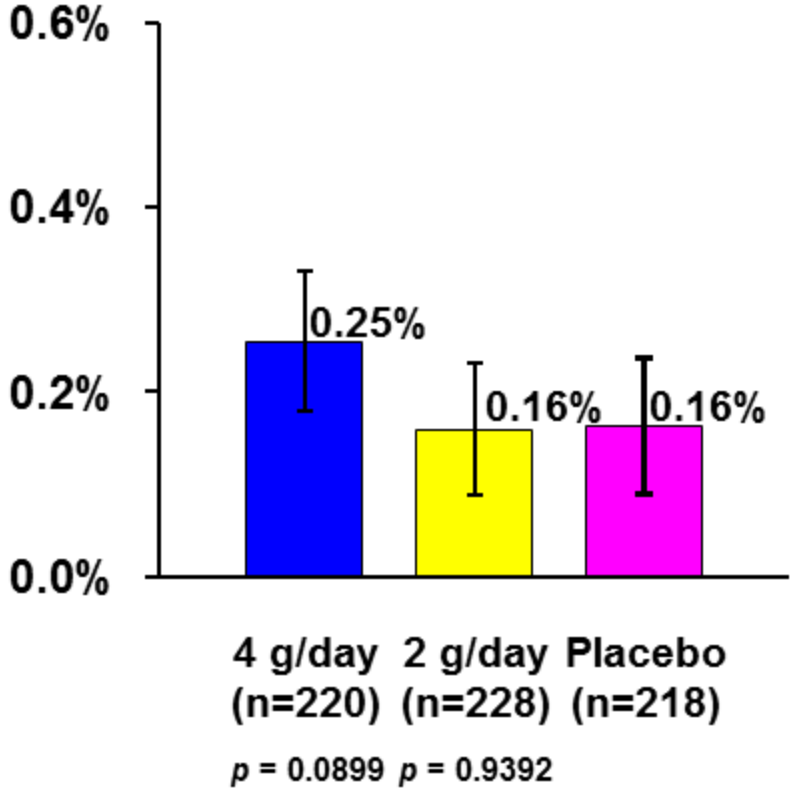
Vascepa Safety Profile was Similar with or without Diabetes

- 73% (n=514) had Type 2 diabetes
- Similar AEs in diabetes patients as seen for entire study

FPG and $HbA1_c$ Levels Compared to Placebo

	FPG (mg/dL)			$HbA1_c$ (%)		
Baseline	133.1	134.8	128.9	6.6%	6.7%	6.5%
Week 12	141.9	138.0	133.7	6.9%	6.8%	6.7%





p-values compared to placebo

Vascepa Post-Marketing Safety Data

	January 1 – September 30, 2013
Vascepa 4 g/day Rx	>125,000
Number of SAEs Reported	1 (GI hemorrhage)
Number of Patients reporting AEs	62
Most Common AEs	Arthralgia (n=9) Diarrhea (n=8) Blood TG increased (n=7)

Vascepa 4 g/day Safety Conclusions

- Well tolerated with AE profile similar to placebo
  - Most common AEs were diarrhea, urinary tract infection, upper respiratory tract infection and nausea
  - Most AEs were mild-to-moderate
- Very few patients withdrew due to AEs
- No new safety signals since initial approval for severe hypertriglyceridemia indication

REDUCE-IT
Trial to Show Reduction of CV Events with VASCEPA

REDUCE-IT is Ph 3B Trial to Assess Vascepa Ability to Reduce CV Events

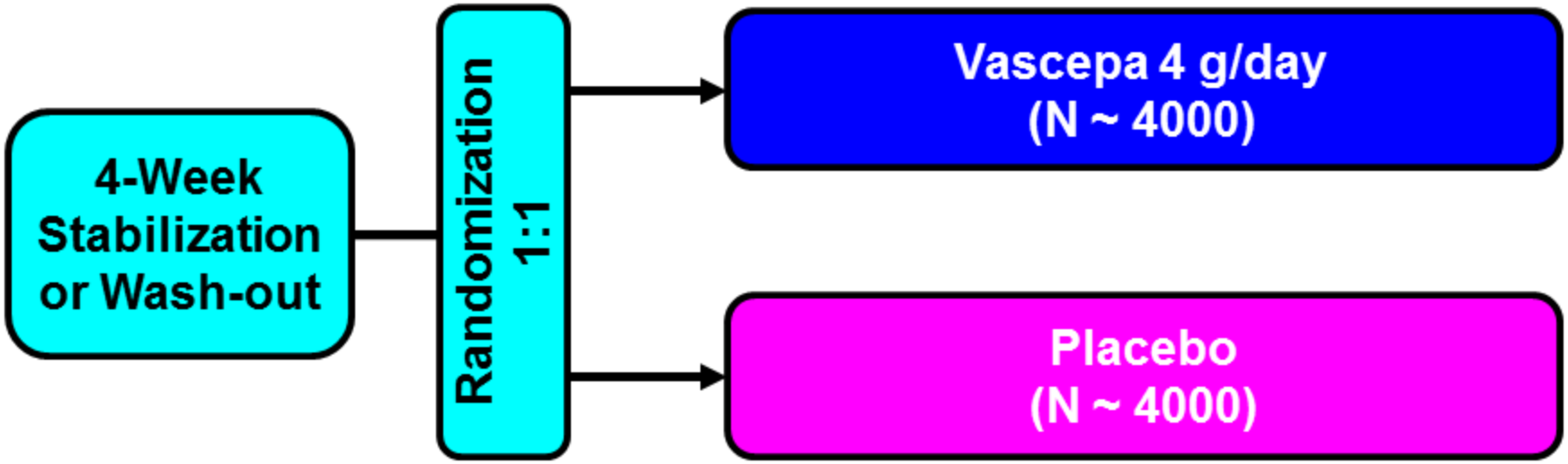
- Randomized, double-blind, placebo-controlled
- Vascepa added to statin therapy in patients with CV disease or CV risk
  - Coronary artery disease
  - Manifestations of CHD
  - Diabetes
- TG 150 to <500 mg/dL
  - SPA amended in May 2013 to modify qualifying TG to 200 to <500 mg/dL

REDUCE-IT to Evaluate Vascepa to Prevent Occurrence of MACE Event

- MACE is composite endpoint
  - CV death
  - Nonfatal MI
  - Nonfatal stroke
  - Coronary revascularization
  - Unstable angina requiring hospitalization
- All potential endpoint events adjudicated by the blinded Clinical Event Committee

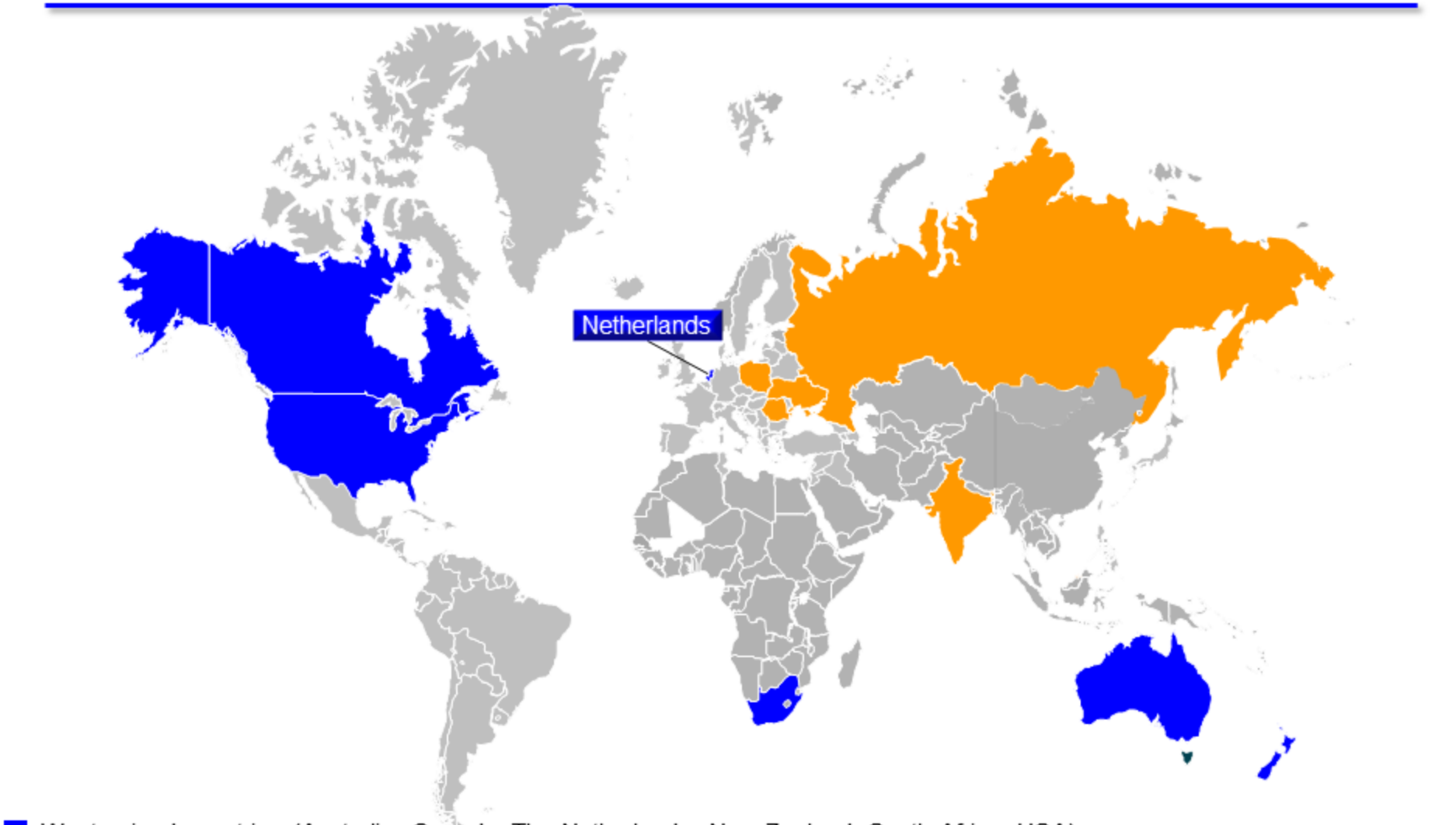
REDUCE-IT is Event-driven Trial

~4-Year Median Treatment and Follow-up



Expected to take ~ 5-6 years from study initiation (Nov 2011) to accrue 1612 events

REDUCE-IT Enrollment Primarily in Westernized Countries (>70%)



REDUCE-IT
Data Monitoring Committee (DMC)

- Quarterly meetings to review blinded and unblinded data
- All DMC meetings to date have recommended continuation of study as planned

REDUCE-IT Enrollment Status Nov 21, 2011 – Oct 4, 2013

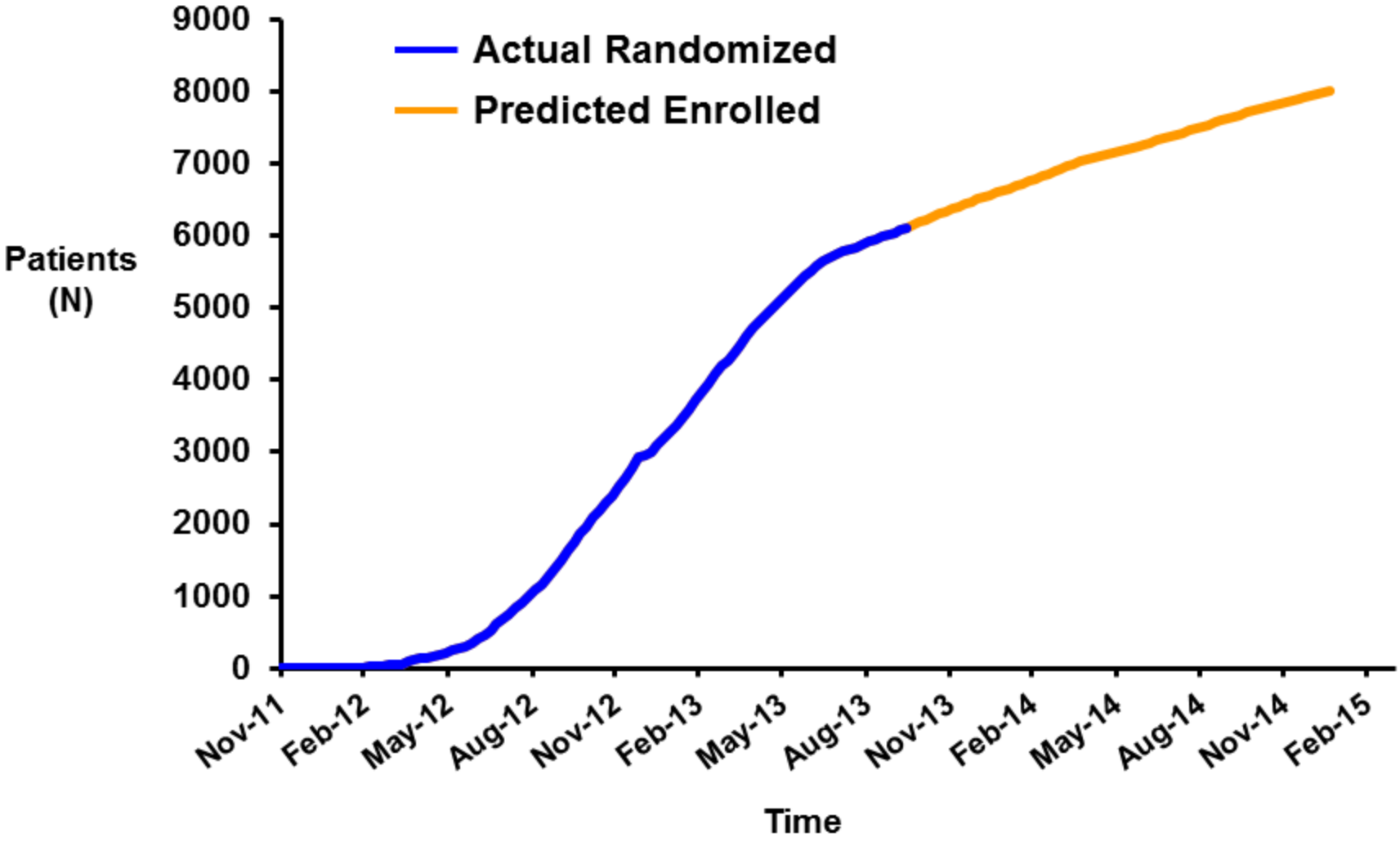
- First patient randomized on Nov 21, 2011
- Total randomized = 6,075 patients
- Qualifying TG levels
  - Median TG = 202 mg/dL
  - Mean TG = 220 mg/dL

REDUCE-IT Patient Exposure to Date

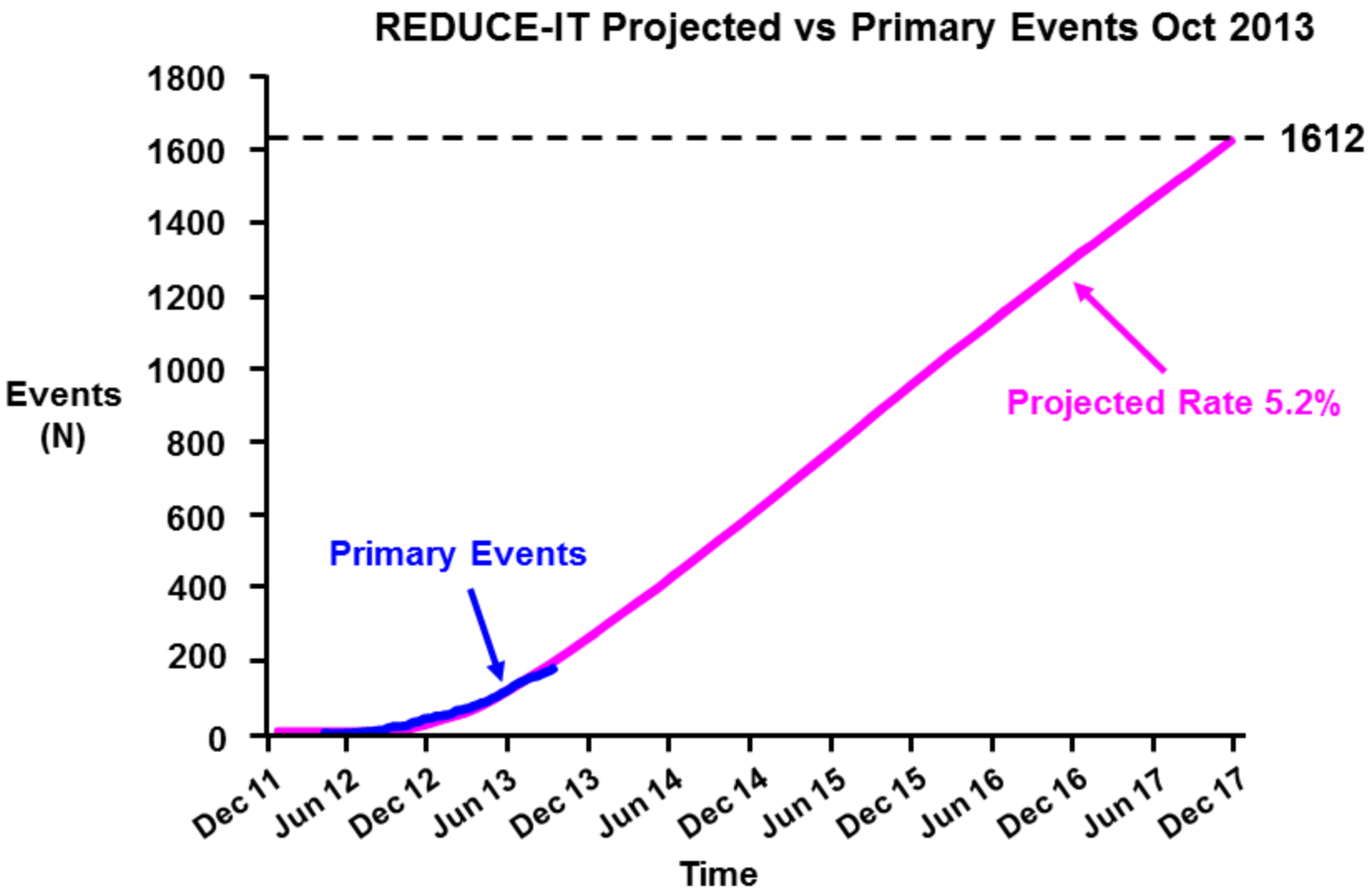
Randomized Vascepa or Placebo Patients + Statin	N=6075*
3 months	5535 (91%)
6 months	4451 (73%)
9 months	3043 (50%)
12 months	1756 (29%)
15 months	575 (10%)
18 months	108 (2%)

* Data as of Oct 04, 2013

REDUCE-IT Enrollment Projections



REDUCE-IT Primary MACE Event Projections



REDUCE-IT Proactive Steps to Optimize Study Conduct

Action	Tactic	Date
Initiate study	Initiated 295 sites in 9 countries	Nov 2011
Increase enrollment	Expanded to 454 sites in 11 countries	Apr 2012
Enrich at-risk population*	Increased TG enrollment threshold to ≥ 200 mg/dL*	May 2013

* Median TG since amendment is 230 mg/dL

REDUCE-IT Aligns with Evolving Regulatory Landscape

- REDUCE-IT is evaluating the ability of Vascepa to reduce first major CV events in high-risk patients on statin therapy
  - SPA agreement
  - >50% enrolled prior to ANCHOR sNDA
  - Safety profile from ANCHOR and MARINE

Vascepa Benefit-Risk

Harold Bays, MD

Louisville Metabolic & Atherosclerosis Research Center

Unmet Need for Patients with Mixed Dyslipidemia and High CHD Risk

- Many statin-treated patients with mixed dyslipidemia have residual CHD risk
  - Elevated TG
  - Elevated apo B
  - Elevated non-HDL-C
- Lowering non-HDL-C is a lipid-centric option to reduce CHD risk in statin treated patients with TG 200 to <500 mg/dL and at LDL-C goal

Guidelines Recommend Reducing Non-HDL-C in Patients with TG 200 to <500 mg/dL

- Many statin-treated patients have persistently elevated TG even when LDL-C levels are at treatment target[1]
- Guidelines recommend reducing elevated non-HDL-C in patients with mixed dyslipidemia[2]
  - NCEP ATP-III, ADA / ACCF, AHA, AACE, TES, The Obesity Society, IAS

1. Wong. *AJC* (2013)
2. NHLBI; Brunzell. *JACC* (2008); Miller. *Circulation* (2011); Jellinger. *Endocrine Practice* (2012); Berglund J. *Clin Endocrinol Metab* (2012); IAS Position Paper

Combination Therapy Often Used in Patients with Mixed Dyslipidemia

- Diet, exercise and statin therapy are the accepted cornerstone of lipid therapy
- Additional TG-lowering therapies added to statins to help reach non-HDL-C goal
  - Nicotinic acid
  - Fibrates
  - Omega acid mixture

NCEP ATP-3. (2004)

Treatment Options for Patients with TG 200 to <500 mg/dL

TG-lowering Therapy	On-label Patient Access	Clinical Outcomes Study in Patients with High TG and High CV Risk
Niacin	Yes	No
Fibrates	Yes	No
Omega Acid Mixture	No	No
Vascepa	Under Review	Ongoing

Practical Challenges of TG-lowering Therapy

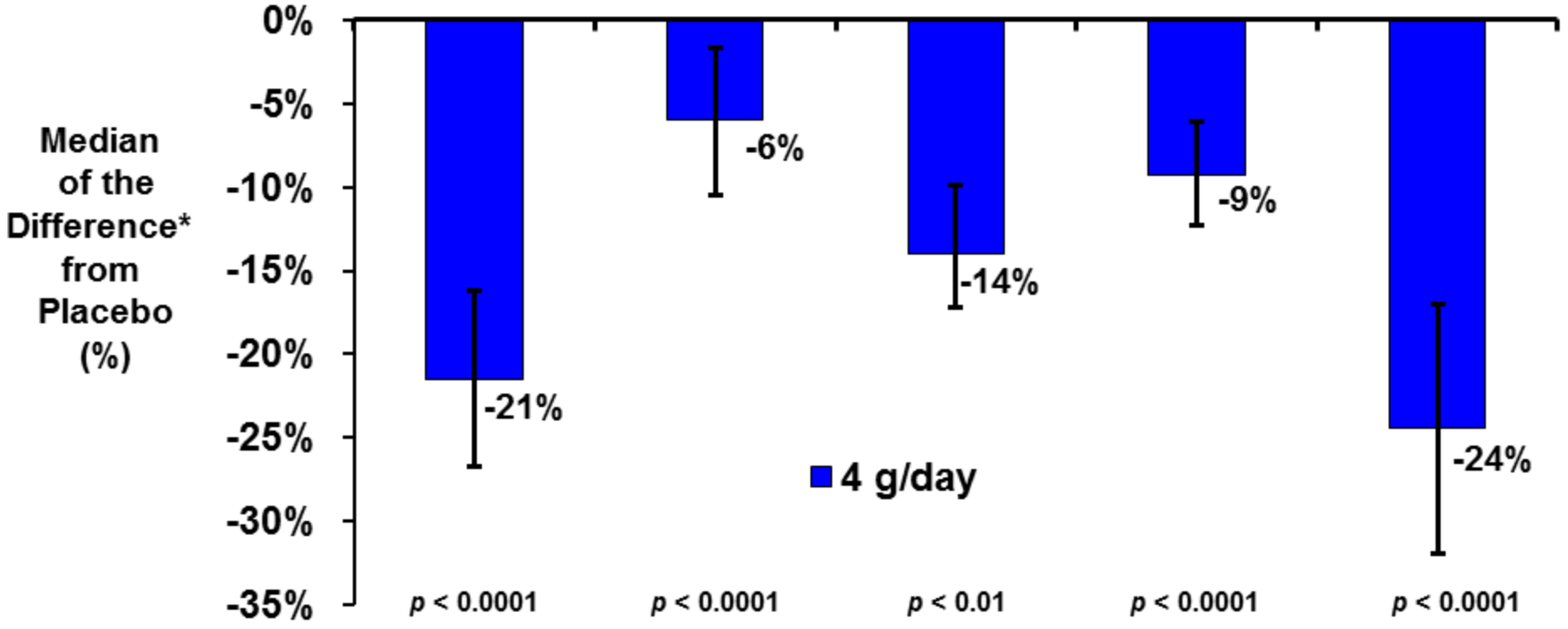
- Nicotinic acid
  - Flushing, liver dysfunction, hyperglycemia (with or without statins)
- Fibrates
  - Warnings for gallstones, renal function, myopathy
- Omega acid mixtures
  - Studied, but not approved for high TG (≥ 200 to < 500 mg/dL)
  - < 500 mg/dL represents majority use

Vascepa is Well Tolerated and Consistent with Omega Acid Class

- Low rate of reported AEs in Vascepa clinical trials
- Omega acid class in general
  - Mild increase in bleeding time
  - Mild increase in glucose without change in HbA1c
- Vascepa
  - Numerical imbalance in bleeding events
  - Numerical increase in glucose without significant change in HbA1c

Vascepa Improves Atherosclerosis Markers in Statin-treated Patients

Vascepa 4 g/day	TG† N=226	LDL-C† N=225	Non-HDL-C† N=226	Apo B† N=217	VLDL-C† N=225
Baseline mg/dL	265	82	128	93	44
Week 12 mg/dL	221	83	122	90	38



p-values compared to placebo; 95% CIs shown; * Hodges-Lehmann median % point estimate of difference
† pre-specified primary and secondary endpoints

ANCHOR Patients have High CV Risk

Characteristic	Vascepa 4 g/day (N=233)	Vascepa 2 g/day (N=236)	Placebo (N=233)
With history of CVD	40%	42%	45%
Diabetes	73%	73%	73%
Hypertension	83%	83%	84%
BMI (kg/m^2)	33	33	33

Priorities in Patient Care

- Patient benefits
  - Treatment according to guidelines
  - Access to safe and effective approved therapies in combination with a statin
  - Forthcoming clinical outcomes study

Vascepa as Adjunct to Statin in Mixed Dyslipidemia and High CHD Risk

- Guidelines suggest that favorable lipid effects should reduce CHD risk
- Use of drug according to labeled use may have advantages over off-label use
- Vascepa approval allows on-label treatment for statin-treated, high CHD risk patients with mixed dyslipidemia
  - Supported by CV outcomes study informed by the favorable ANCHOR study results
  - Substantially enrolled

Vascepa® (icosapent ethyl) as an adjunct to diet and in combination with a statin to reduce TG, non-HDL-C, ApoB, LDL-C, TC, and VLDL-C in adult patients with mixed dyslipidemia and CHD or a CHD risk equivalent

Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)

October 16, 2013

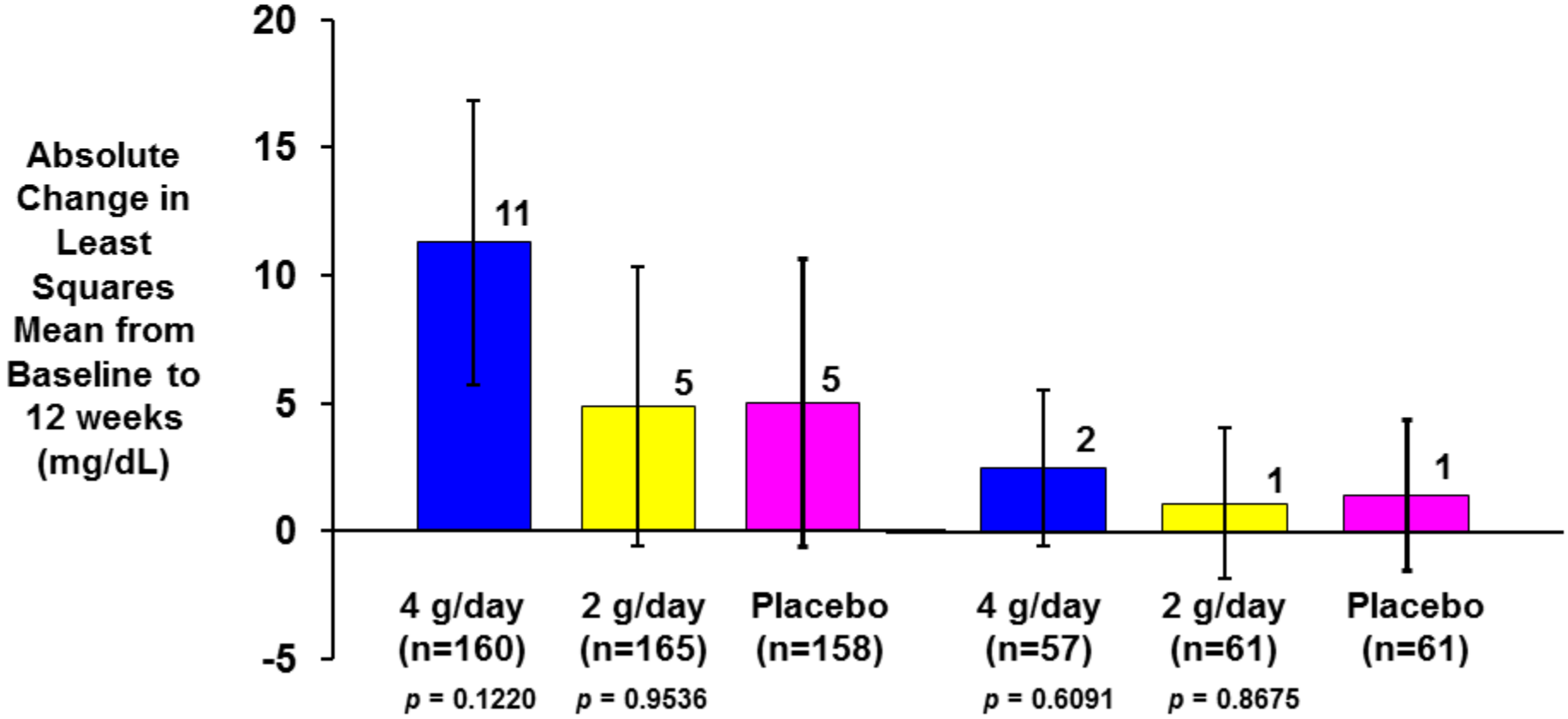
Backup Slides

ANCHOR
Bleeding Related AEs

	ANCHOR					
	4g/day		2g/day		Placebo	
AE Preferred Term	N=233	(%)	N=236	(%)	N=233	(%)
Subjects with Bleeding-related AE's	6	(2.6%)	7	(3.0%)	4	(1.7%)
Total Bleeding Events	6	(2.6%)	9	(3.8%)	4	(1.7%)
Anemia	2	(0.9%)	1	(0.4%)	0	(0%)
Hematochezia	1	(0.4%)	0	(0%)	1	(0.4%)
Contusion	0	(0%)	2	(0.8%)	2	(0.9%)
Hematoma	0	(0%)	1	(0.4%)	0	(0%)
Infusion Site Hematoma	0	(0%)	0	(0%)	1	(0.4%)
Spontaneous Hematoma	0	(0%)	1	(0.4%)	0	(0%)
Subdural Hematoma	0	(0%)	1	(0.4%)	0	(0%)
Traumatic Hematoma	2	(0.9%)	1	(0.4%)	0	(0%)
Subarachnoid Hemorrhage	1	(0.4%)	1	(0.4%)	0	(0%)
Uterine Hemorrhage	0	(0%)	1	(0.4%)	0	(0%)

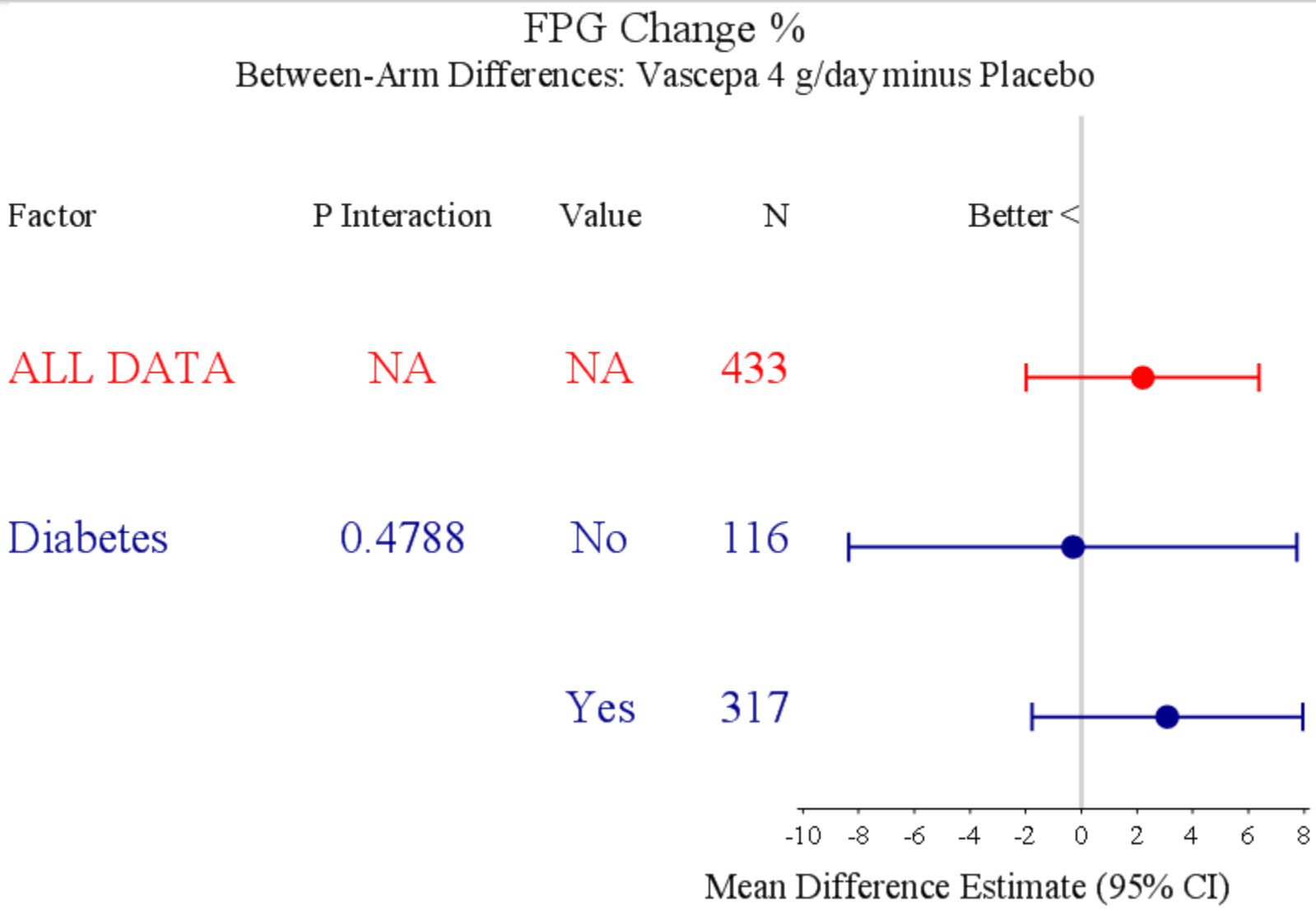
ANCHOR
FPG Levels in Patients with Diabetes and Non-Diabetes

	Diabetes			Non-Diabetes		
Baseline mg/dL	143	146	140	107	105	102
Week 12 mg/dL	154	150	145	108	105	104

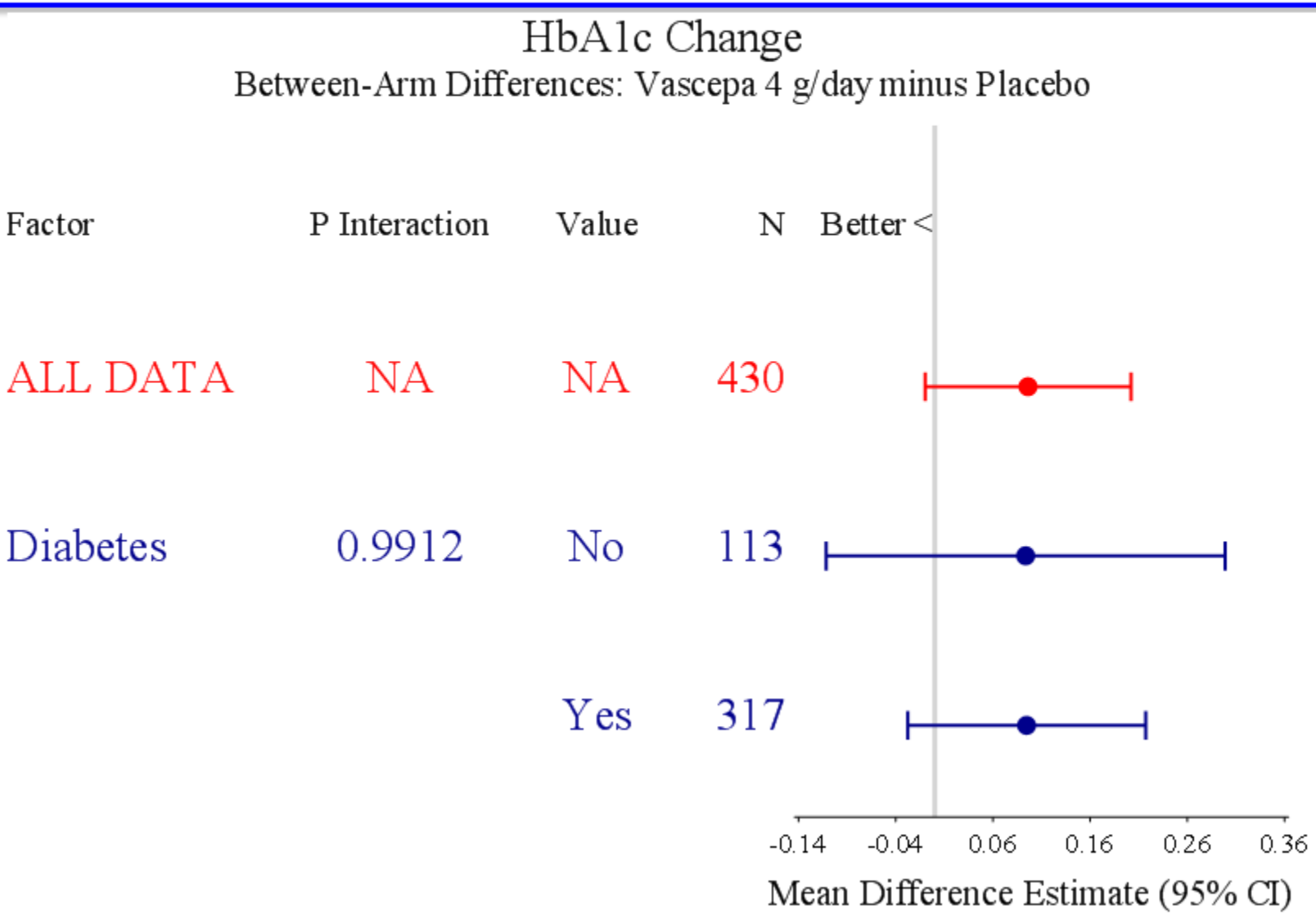


P-values compared to placebo

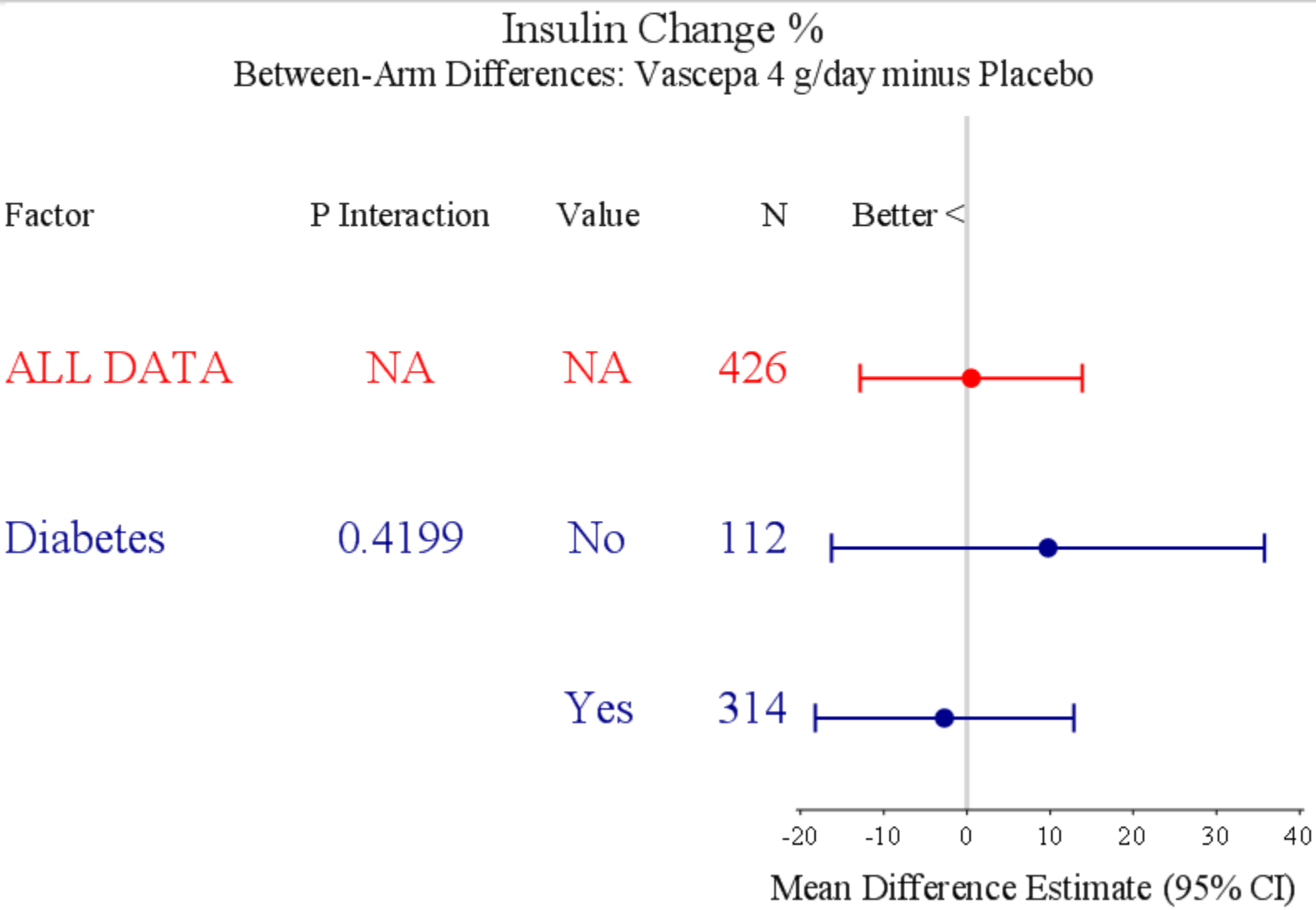
FPG Response (4g vs. PBO): With and Without Diabetes



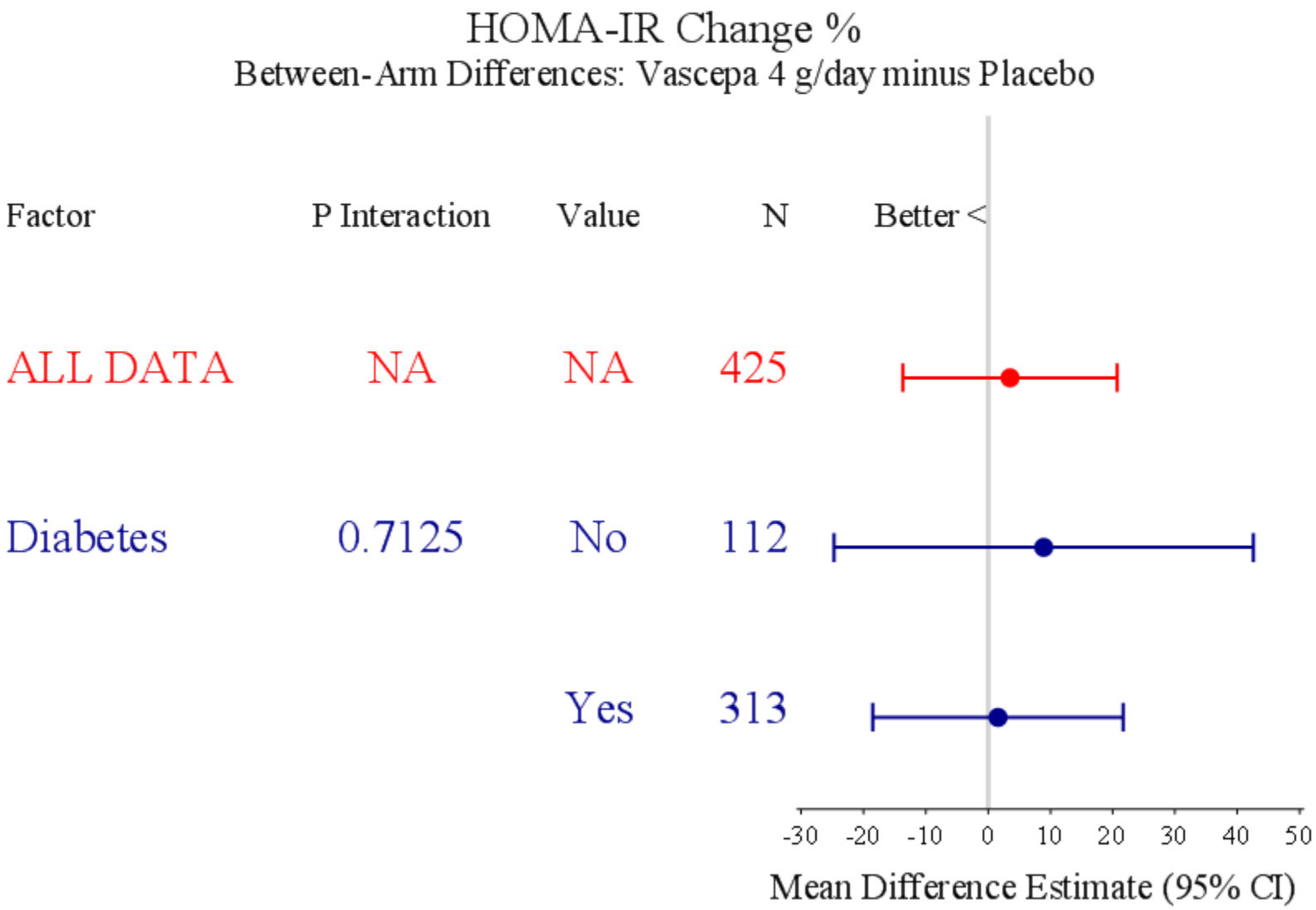
HbA1c Response (4g vs. PBO): With and Without Diabetes



Insulin Response (4g vs. PBO) : With and Without Diabetes



HOMA-IR Response (4g vs. PBO): With and Without Diabetes



Jelis Subanalysis in Non-EPA and EPA Treatment Groups

	NG (n=14080)		IGM (n=4565)	
	Non-EPA (n=7057)	EPA (n=7023)	Non-EPA (n=2262)	EPA (n=2303)
Glucose metabolism				
FPG (mg/dL)	97±17	98±15	141±46	142±45
HbA1c (%)	5.4±0.8	5.4±0.7	6.9±1.4	7.0±1.4

Data are reported as percentage or mean ±standard deviations, unless otherwise indicated.
NG, normal glycemia; IGM, impaired glucose metabolism.

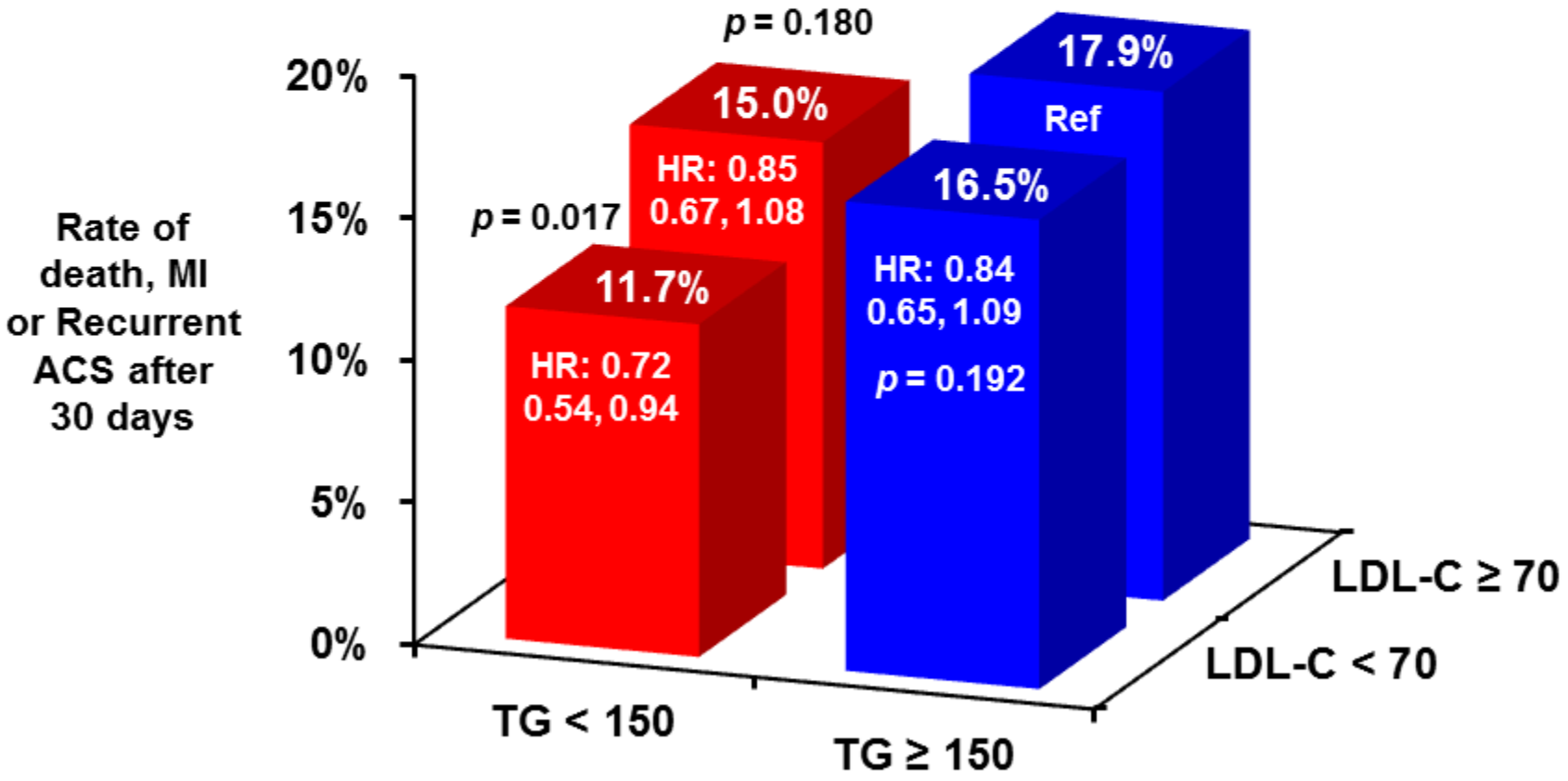
Oiwaka. *Atherosclerosis* 2009; 206:535–539.

Few African Americans Randomized: High Screen Failure Rates and Low TG

- African Americans also had higher rates of CK out of range, HbA1c out of range and positive Hep B/C antibody

Screened	Overall	White	African American	Asian	Hispanic
Total Screened	2309	2064	155	39	319
% Screen failure	70%	67%	92%	79%	74%
Randomized	702	676	12	8	83
TG out of range	51%	50%	54%	61%	47%
Median TG (mg/dL)		173	134	161	169
CK out of range			4%		
Positive Hep B/C Ab	1%	1%	6%		
HbA1c out of range	9%	9%	14%		15%

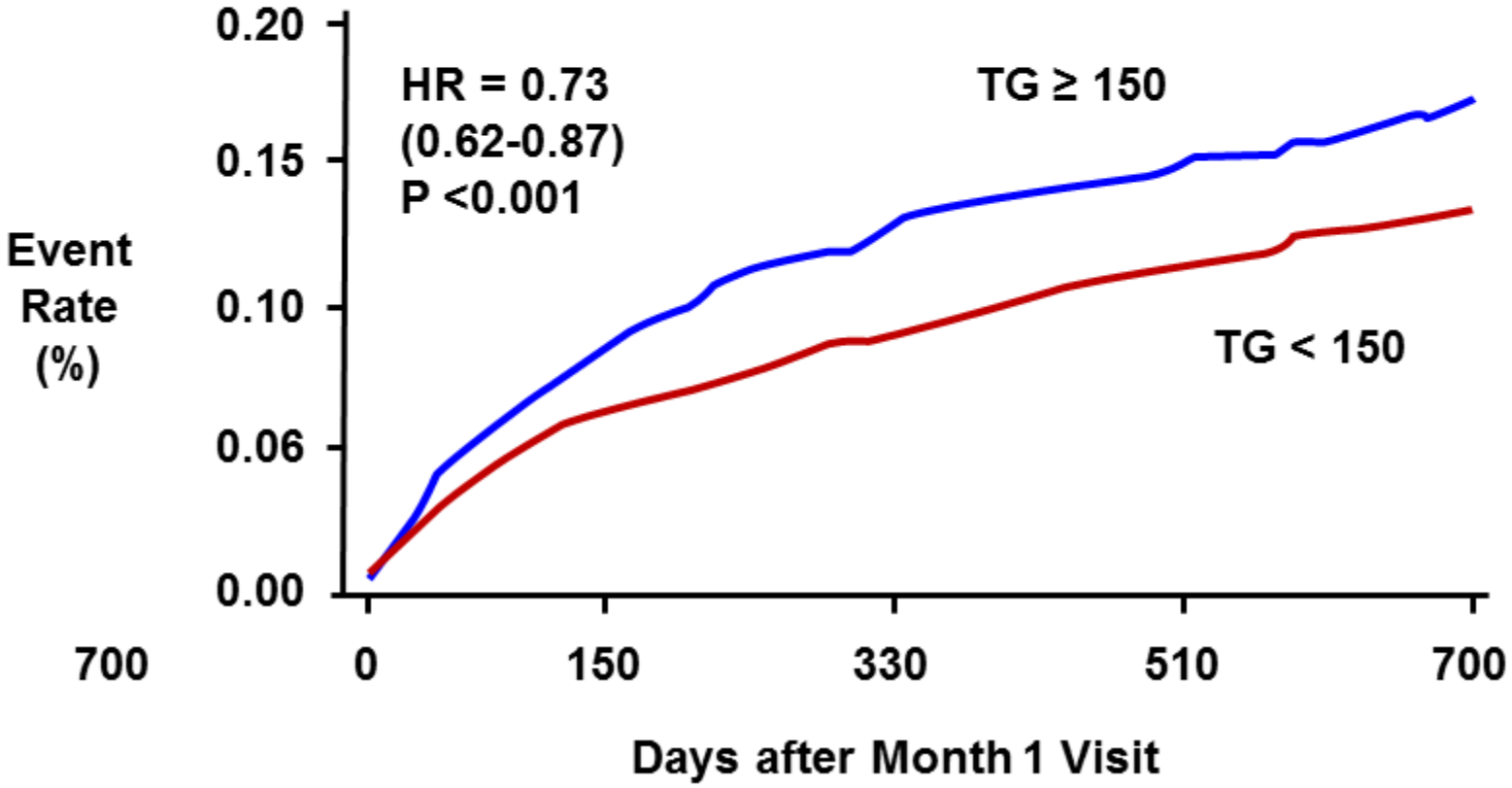
PROVE-IT: Low On Treatment TG Reduces CHD Risk Independent of LDL-C



Miller 2008 JACC; 51(7)724-730

Low on Treatment TG Levels Reduce CHD Risk

Each 10 mg/dL reduction in TG equates to a 1.8% reduction in CHD risk



Systematic Evaluation of Mineral Oil

- Historical precedent
  - Mineral oil studies
  - Mixed dyslipidemia studies
- Inhibition of statin absorption
- Underlying drift of lipid values in the placebo patients

Effects on Lipids Are Variable in Mineral Oil Placebo Arm of Clinical Trials

Author	n*	Daily Dose	Duration	Patient Population	Lipid-lowering agents?	TG	LDLc	nHDLc	HDLc	TC
Ballantyne** 2012 (ANCHOR)	227	4 g	12 wks	TG ≥200 mg/dL	Required	↑	↑	↑	↑	↑
Bays** 2011 (MARINE)	75	4 g	12 wks	TG ≥500 md/dL	Allowed	↑	↓	↑	No change	↑
Kabir 2007	14	3 g	8 wks	DM Type 2	Allowed	↑	No change	↑	↑	↓
Yang 1999	20	5 g	16 wks	Atopic dermatitis	--	No change	↑	--	--	--
Peet** 2002	6	4 g	12 wks	Schizophrenia	--	↑	--	--	--	--
Mohammadi 2012	31	2g	8 wks	Polycystic ovary syndrome	--	↓	No change	--	↑	↓
Lemos 2012	75	2 g	17 wks	Renal Failure	--	↑	↓	--	↑	↓
Emsley** 2008	33	2 g	12 wks	Schizophrenia	--	↓	No change	↑	↓	--
De Truchis 2007	62	2 g	8 wks	HIV antiviral therapy TG >200 mg/dL	Allowed	↑	--	--	↑	---

•n represents subjects in the mineral oil group

** study involved icosapent ethyl and/or placebo supplied by Amarin or its predecessors

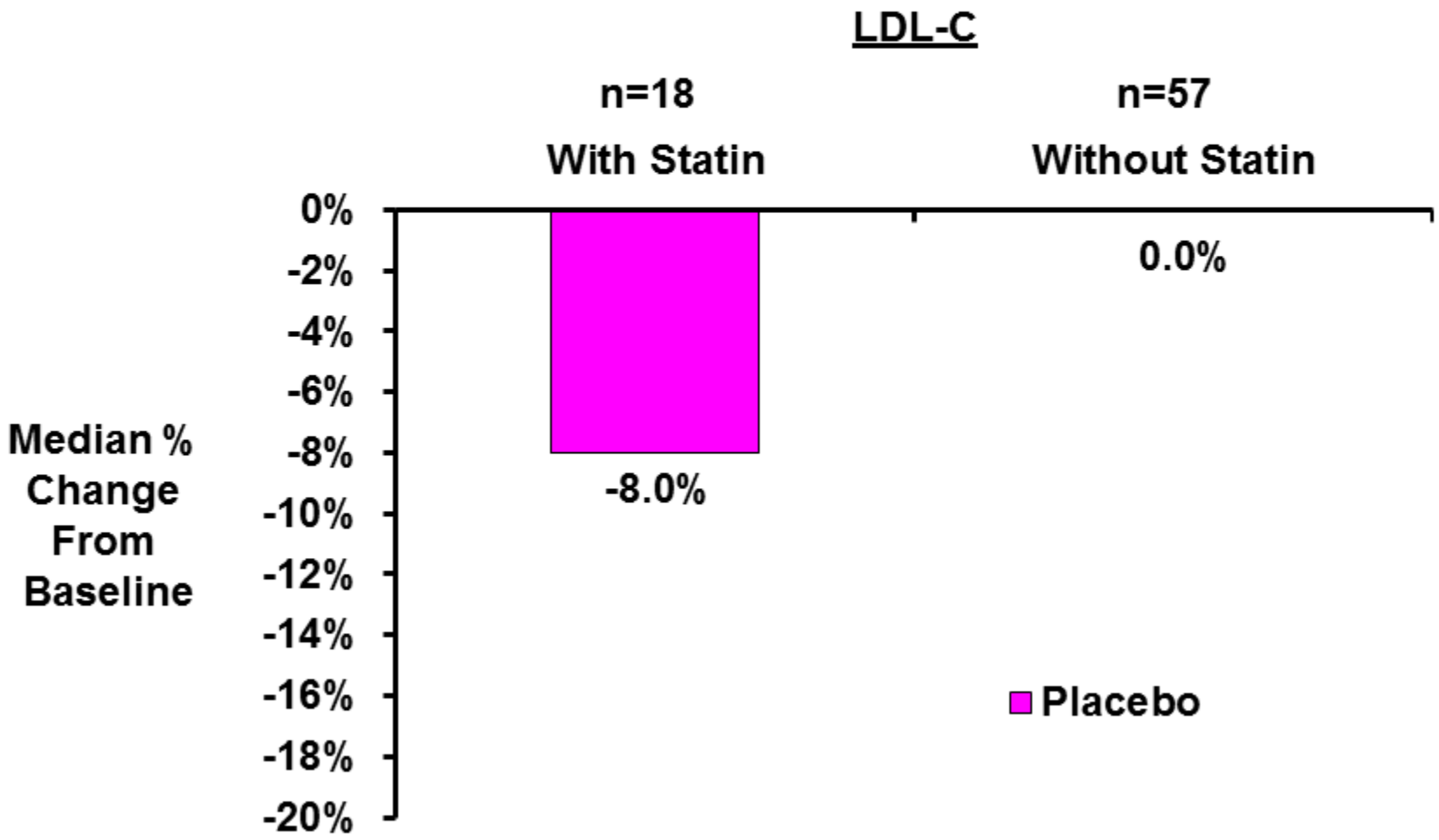
Mixed Dyslipidemia Studies Often Show Variability in Placebo Group

High Triglycerides Population	Placebo Substance	Duration of PBO	N	% Change TG	% Change LDL-C	% Change Non-HDL-C
350-499[1]	Tablet	8 wks	28	-0.5	+12.0	n/a
Hyper-triglyceridemia[2]	Solid	8 wks	49	-17	+11	+2
mixed dyslipidemia[3*]	Tablet	24 mos	329	-2 ** approx	+10 * approx	+5 * approx
ANCHOR	Mineral Oil	12 wks	227	+6%	+9%	+10%
Primary Htg[4]	Tablet	6 wks	26	+1	+5	+2
Hyper-TG (200-799)[5]	Solid	8 wks	35	+1	+3.6	+1.4
Hyper-TG in T2DM (150-699)[6]	Solid	6 wks	144	-0.1	+2.3	+1
mixed dyslipidemia[7]	Tablet	16 wks	73	+12	+1	n/a
Type IV[8]	Tablet	6 wks	74	-9	+1	+1
200-499[9]	Corn Oil	8 wks	132	-6.3	-2.8	-2.2

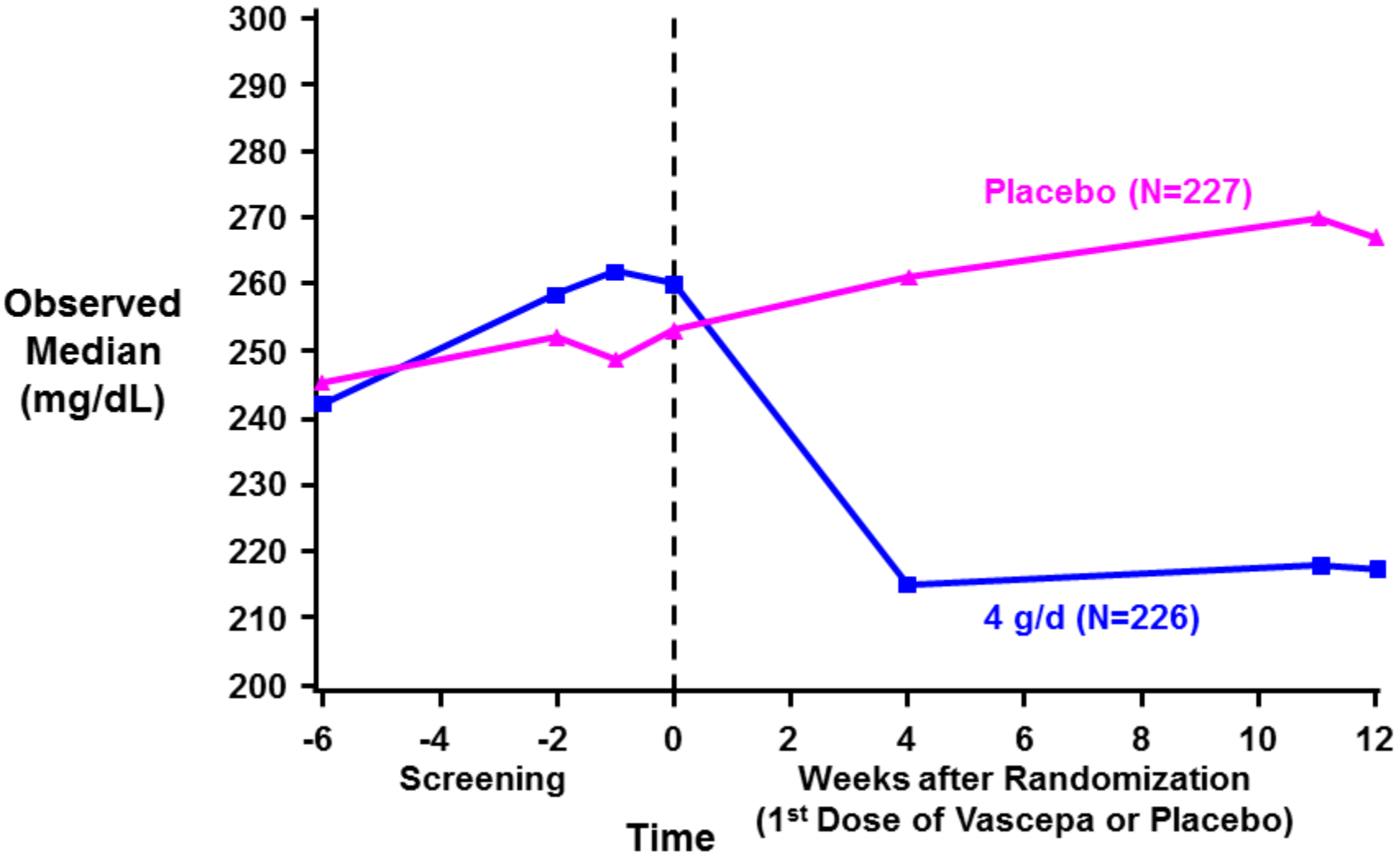
*FDA Briefing Document cites results at 13 week time point (median change from baseline): TGs -2%; LDL-C +2%, non-HDL-C 0%

1) TRICOR PI (2011); 2) Koh (2012); 3) Davidson (2013); 4) Crestor PI (2013); 5) Saito, 2007; 6) Miller (2004); 7) Niaspan PI (2013); 8) Zocor PI (2012); 9) LOVAZA PI (2012)

Mineral Oil Did not Seem to Inhibit Statin Absorption in MARINE



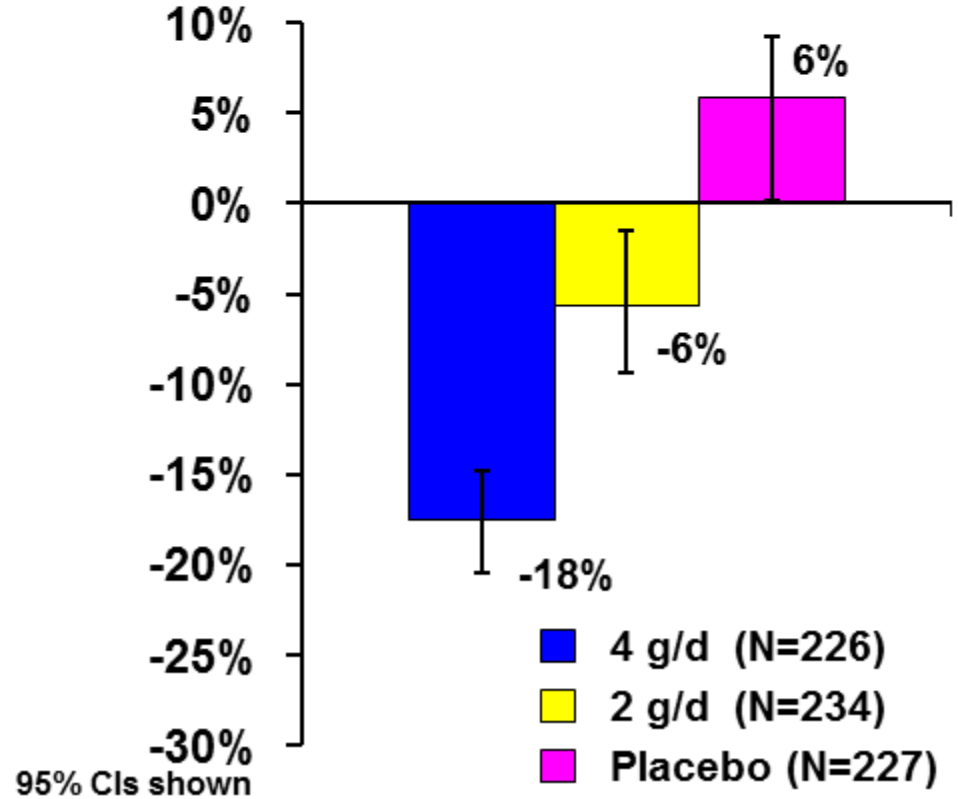
Placebo TG Arm Drift Continues From Screening Through End of Treatment



Vascepa Significantly Improves TG Levels in Patients on Statins

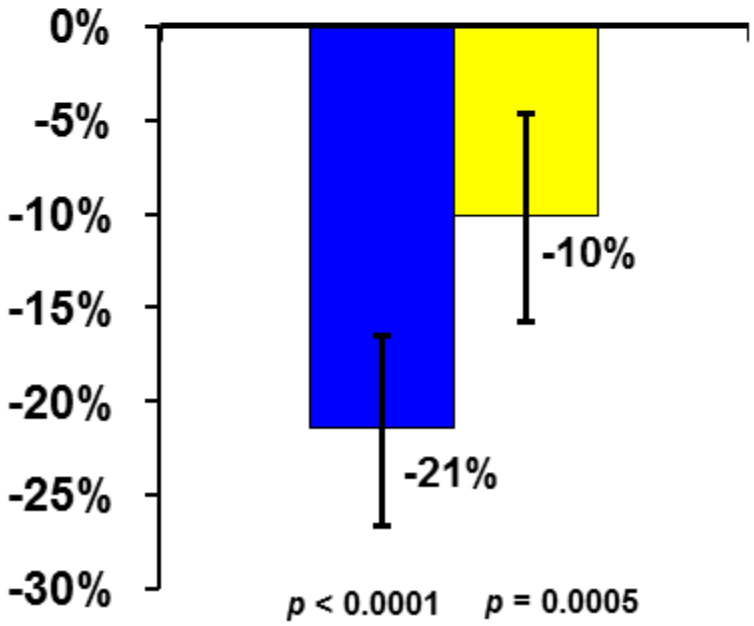
Median % Change from Baseline TG

Baseline mg/dL	265	254	259
Week 12 mg/dL	221	244	270



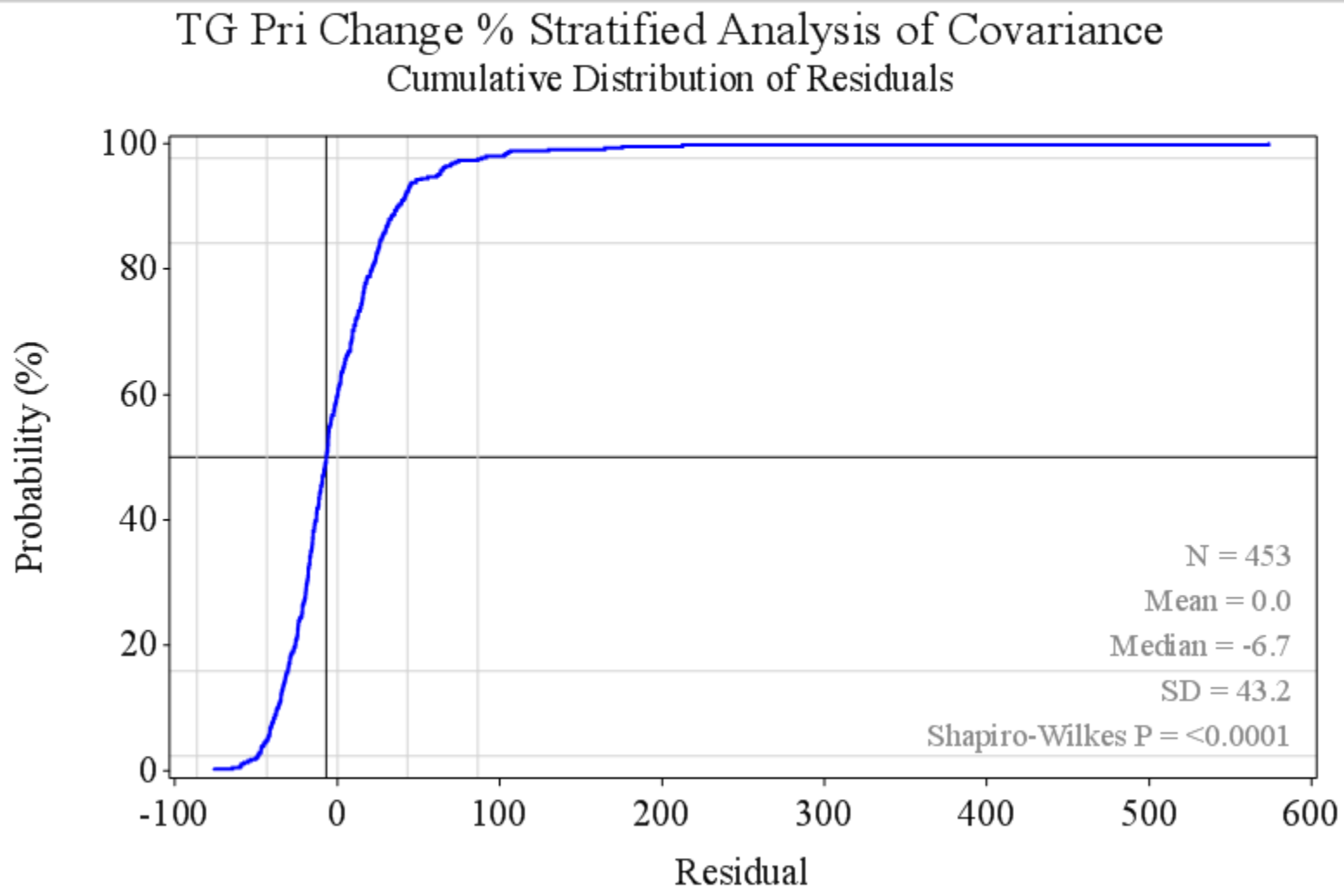
95% CIs shown
p-values compared to placebo

Median of the Difference* from Placebo



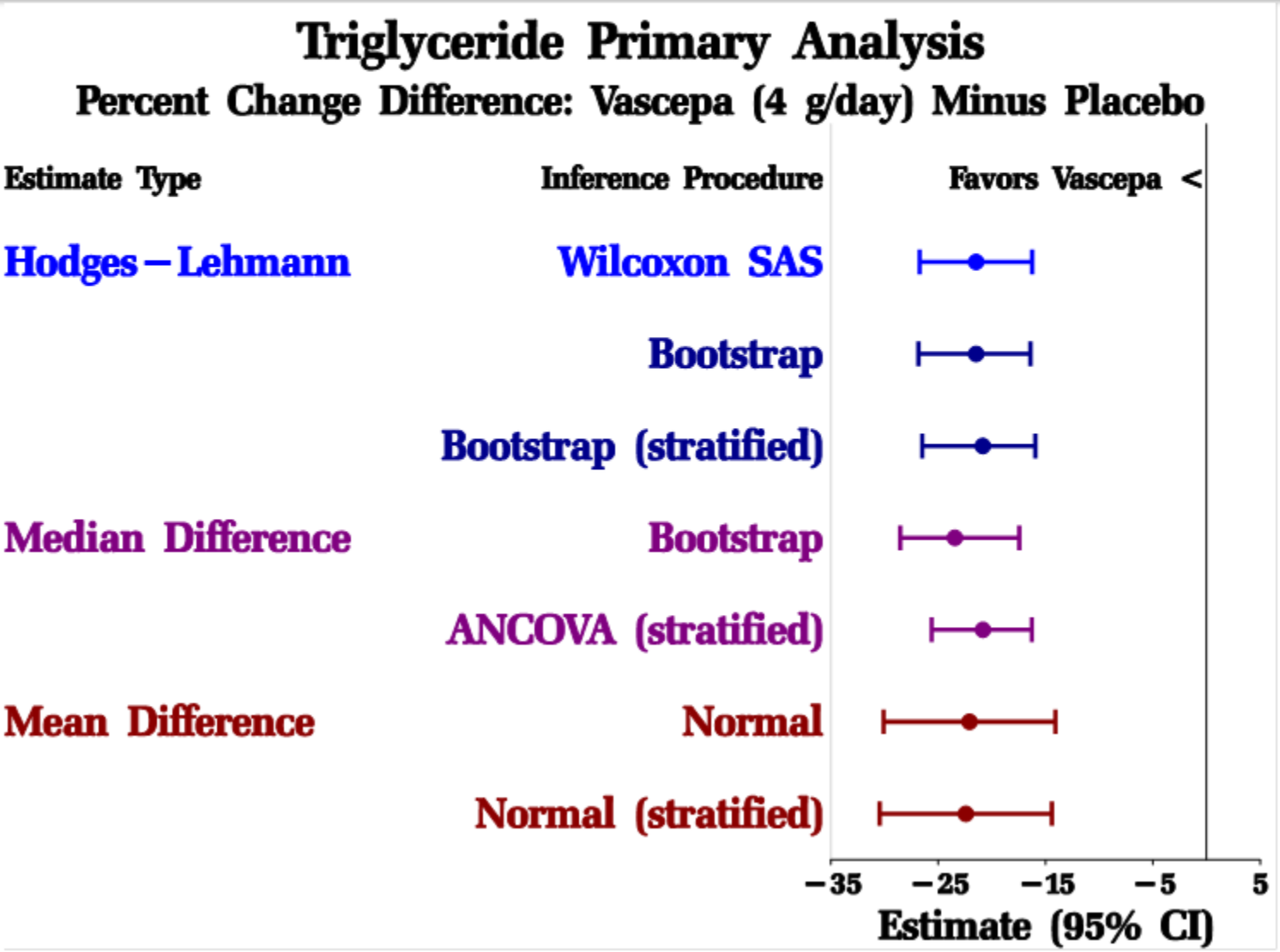
* Hodges-Lehmann median % point estimate of difference

TG Response: Shapiro-Wilk Test for Normality

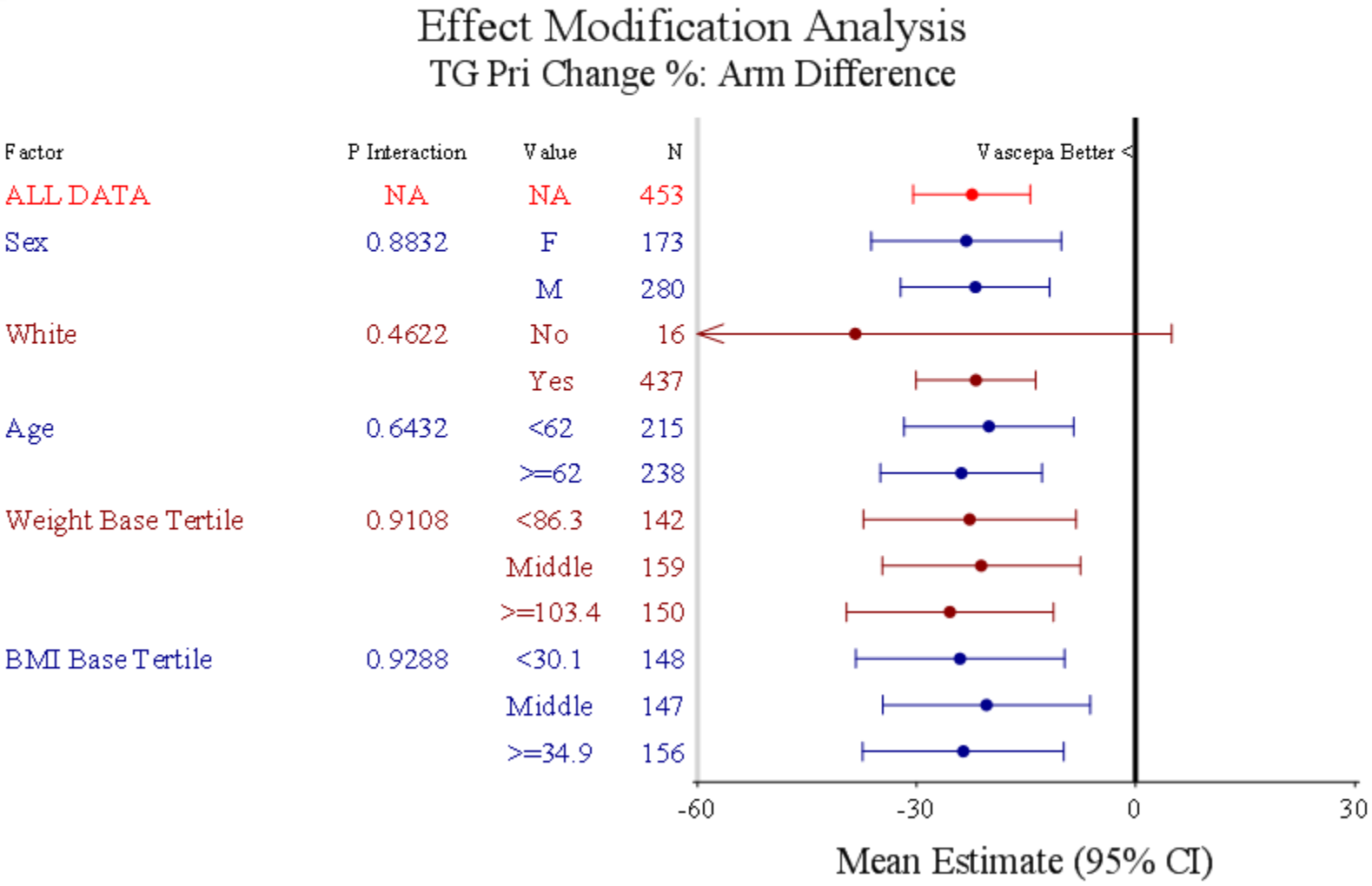


Covariate(s) beyond group indicator: stratc

TG Primary Analysis: Similar Results with Different Statistical Methods

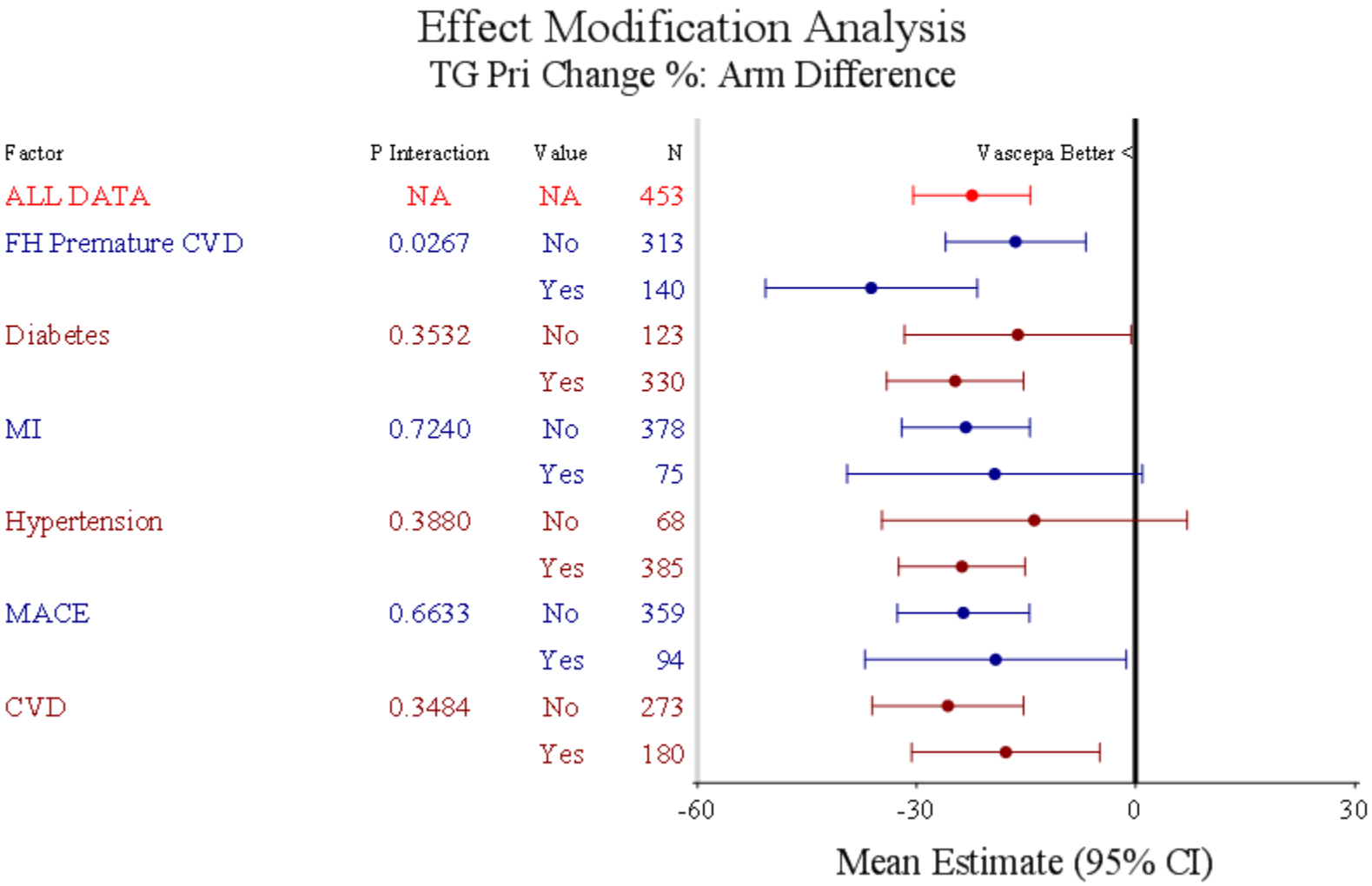


Effect Modifier Analysis of Primary Endpoint



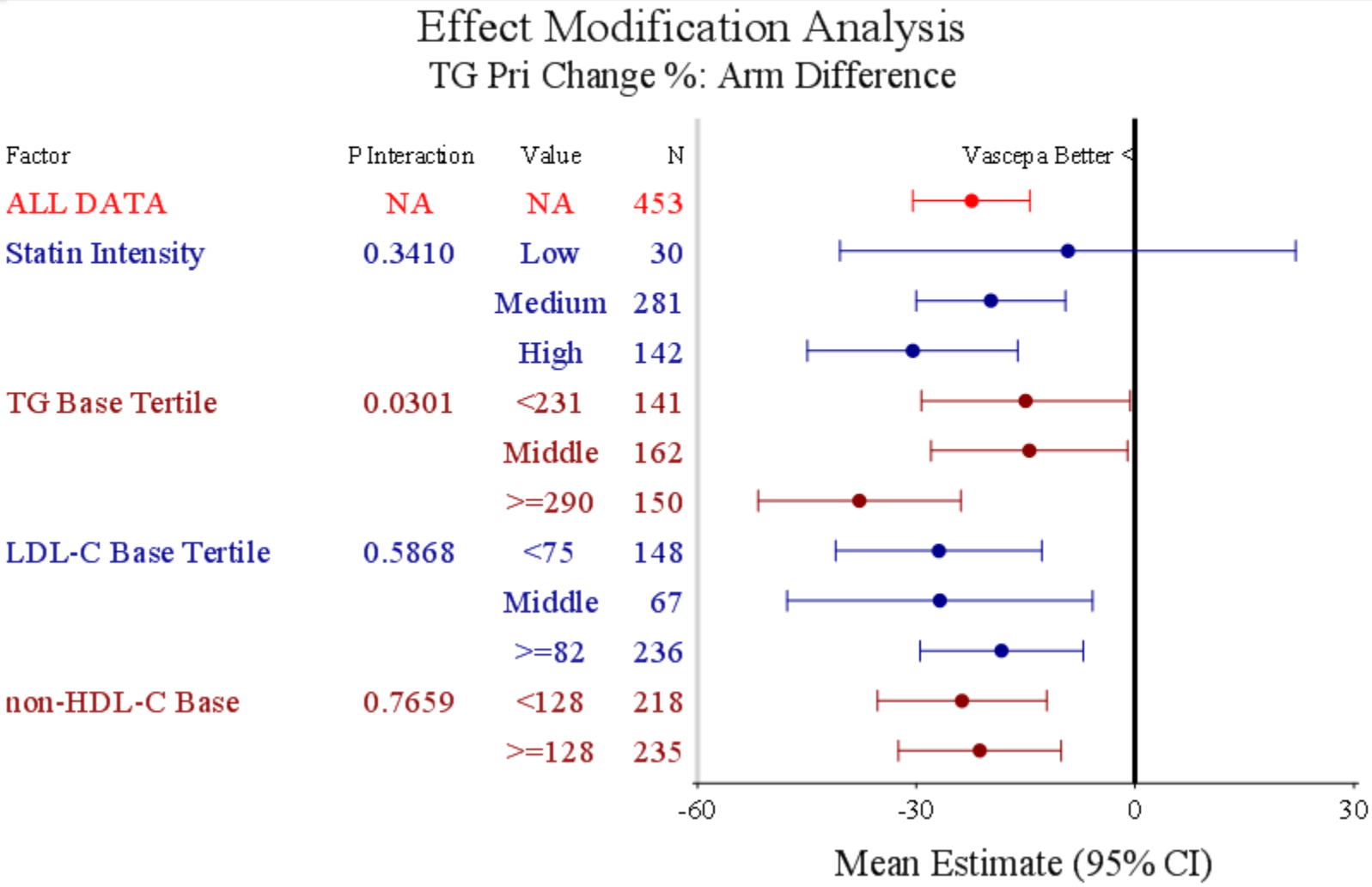
Stratified by Statin / Diab / Sex

Effect Modifier Analysis of Primary Endpoint



Stratified by Statin / Diab / Sex

Effect Modifier Analysis of Primary Endpoint

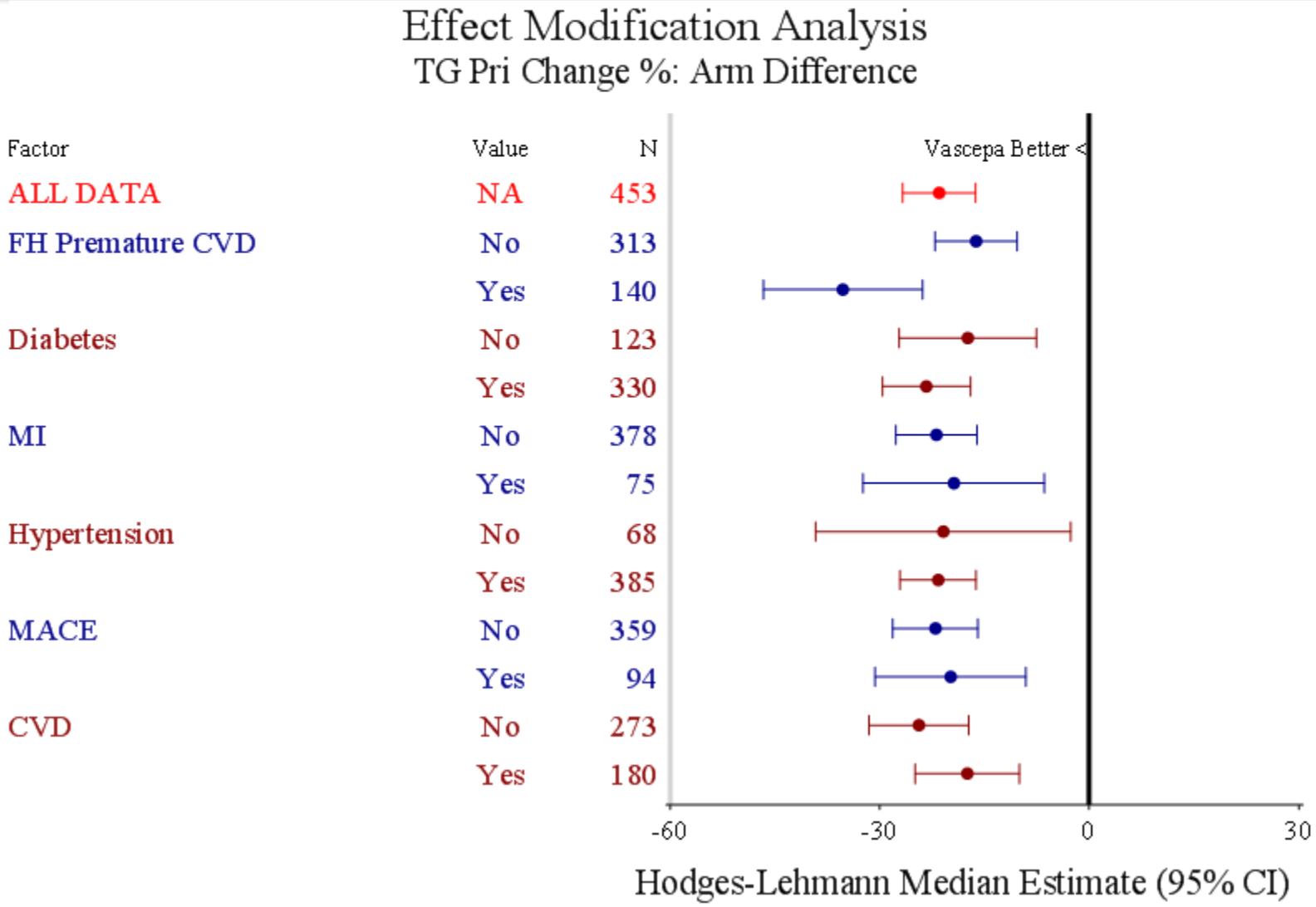


Stratified by Statin / Diab / Sex

REDUCE-IT : MACE and Expanded MACE

- MACE
  - CV-related death
  - nonfatal stroke
  - nonfatal myocardial infarction
- Expanded MACE
  - Hospitalization for unstable angina
  - hospitalization for coronary revascularization

Effect Modifier Analysis of Primary Endpoint



ANCHOR
Bleeding-related Adverse Events

Preferred Bleeding Term (%)	Double-blind Treatment 4 g/day (N=233)	2 g/day (N=236)	Placebo (N=233)
Total Subjects with Bleeding-related AE's	2.6	3.0	1.7
Total of Bleeding-related AEs			
Anemia			
Spontaneous hematoma			
Hematochezia	0.4	0	0.4
Contusion	0	0.8	0.9
Hematoma	0	0.4	0
Infusion Site Hematoma	0	0	0.4
Subarachnoid Hemorrhage	0.4	0.4	0
Subdural Hematoma	0	0.4	0
Traumatic Hematoma	0.9	0.4	0
Uterine Hemorrhage	0	0.4	0

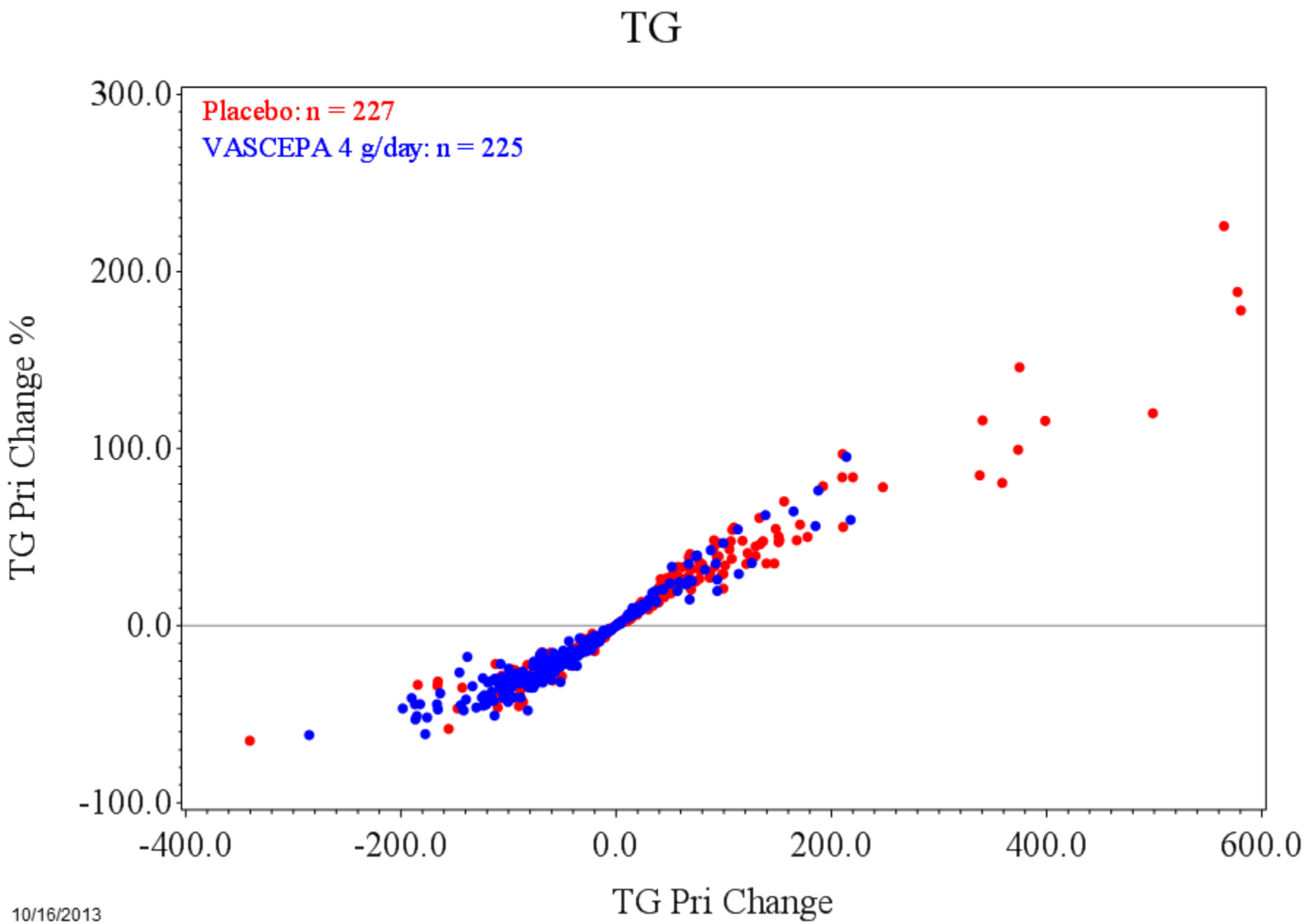
Difference from placebo = 0.86
(95% CI of –2.03% to 3.25%)

All patients with bleeding event were taking anti-platelet or anti-coagulant therapy

ANCHOR
Bleeding Events in Patients Taking Platelet Inhibitors

Therapeutic Class Preferred Term	4 g/day (n=233)		2 g/day (n=236)		Placebo (n=233)	
	n	(%)	n	(%)	n	(%)
Patients on Platelet aggregation inhibitors excl. heparin	138	(59.2%)	135	(57.2%)	141	(60.5%)
Patients on Platelet aggregation inhibitors with Bleeding events*	6	(4.3%)	7	(5.1%)	4	(2.8%)

*% is based on the number of patients on platelet aggregation inhibitors excl. heparin


TG
Placebo: n = 227
VASCEPA 4 g/day: n = 225
300.0
200.0
100.0
0.0
-100.0
TG Pri Change %
-400.0
-200.0
0.0
200.0
400.0
600.0
TG Pri Change

10/16/2013